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Approach to Early Barrett's Cancer

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Abstract. Because of effective surveillance programs in patients with known Barrett's esophagus, adenocarcinoma of the distal esophagus is increasingly diagnosed at early stages. With the introduction of limited surgical and endoscopic treatment modalities, the need for radical esophagectomy and extensive lymphadenectomy in such patients has been questioned. When selecting the approach to early Barrett's cancer, the precancerous nature of the underlying Barrett's esophagus, the frequent multicentricity of neoplastic alterations within the Barrett mucosa, the inaccuracy of current staging modalities, and the presence of lymph node metastases should be taken into account. Invasiveness and morbidity of the procedures, as well as quality of life aspects, should also be considered. From an oncologic point of view the minimum extent of a resection for early Barrett's cancer should include a full-thickness removal of the entire segment of the distal esophagus covered by intestinal metaplasia together with a regional lymphadenectomy. In appropriately selected patients this can be achieved by a limited surgical procedure involving transhiatal resection of the distal esophagus, but not by endoscopic mucosal ablation or endoscopic mucosa resection. Our experience with 49 limited surgical resections with regional lymphadenectomy indicates that this procedure is oncologically adequate and safe. Reconstruction with an interposed jejunal loop prevents postoperative gastroesophageal reflux and is associated with good quality of life. In contrast, endoscopic interventions are plagued by a high tumor recurrence rate, probably from persistence of Barrett's mucosa and gastroesophageal reflux.

The precancerous nature of specialized intestinal metaplasia of the distal esophagus (the so-called Barrett's esophagus) has been clearly established. The risk of developing an esophageal adenocarcinoma is in the order of 0.5% to 1.5% per year of follow-up in such patients [1]. Although long-lasting and severe gastroesophageal reflux has been identified as the major predisposing factor for the development of Barrett's esophagus and esophageal adenocarcinoma, it is unclear at present whether progression to invasive carcinoma can be halted by aggressive medical or surgical treatment of gastroesophageal reflux once a Barrett's esophagus has developed [1].

Close endoscopic surveillance is therefore widely recommended in patients with known Barrett's esophagus. Although the overall impact and cost-efficacy of surveillance endoscopy has been questioned, tumors detected in patients under endoscopic surveillance are usually in an early stage [2, 3]. In our own experience, the prevalence of early tumor stages among all resected esophageal adenocarcinoma has increased from less than 20% before 1992 to about 40% since 1997 (Fig. 1) [4].

Because the progression from intestinal metaplasia to invasive adenocarcinomais a multistep process, various stages of preneoplastic and early neoplastic alterations of the Barrett mucosa are being diagnosed more and more often with endoscopic biopsies in patients with no macroscopically visible lesions [5]. As a consequence, the standard therapy for early esophageal adenocarcinoma—i.e., radical esophagectomy with extensive lymph node dissection—has been challenged. Because, even in experienced hands, esophagectomy with extensive lymphadenectomy is associated with substantial morbidity and a compromised quality of life, more limited surgical and endoscopic procedures have been introduced as alternatives for patients with early neoplastic changes in Barrett's carcinoma [5–11]. A comparison of these treatment modalities is, however, currently hampered by confusion in the terminology used to describe the early malignant changes for which they are applied.

Dysplasia, Carcinoma In Situ, Intraepithelial Neoplasia, and Early Barrett's Cancer

The terms *dysplasia, atypia, carcinoma in situ*, and *mucosal carcinoma* are frequently used to describe pre-neoplastic and early neoplastic changes in the Barrett mucosa. There are, however, large discrepancies among pathologists in the interpretation and application of these terms [12]. The clinical use of these terms as basis for therapeutic decision making and comparison of treatment results is therefore questionable. In an attempt to resolve this problem, an international consensus conference of pathologists [13] and the recent World Health Organization classification of tumors of the digestive tract [14] have suggested that the term *intraepithelial neoplasia* be adopted to describe pre-invasive neoplastic change of the epithelium. This term was chosen to indicate that a mucosal alteration carries a clear risk of progression to invasion and metastases and to differentiate these changes from reactive or regenerative alterations. On blinded review of "representative slides," the

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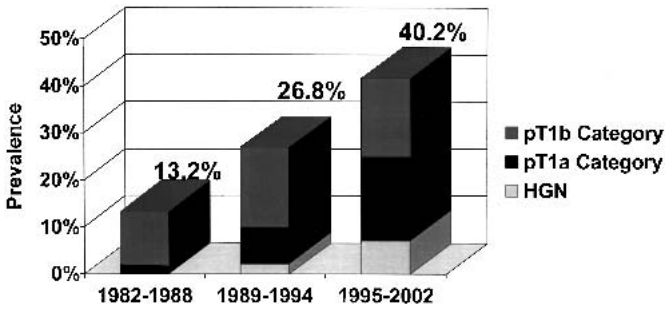

Fig. 1. Increasing prevalence of early tumor categories among all patients undergoing surgical resection for esophageal adenocarcinoma at Technische University Munich.

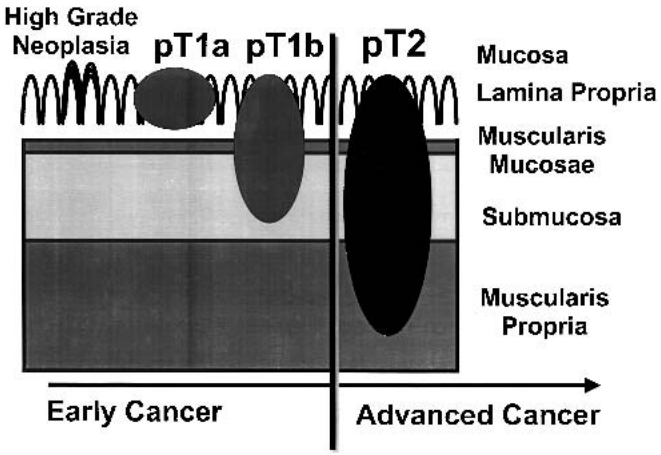

Fig. 2. Schematic depiction of the entities encompassing "early Barrett's carcinoma."

concordance of pathologists is, however, still surprisingly poor, even in differentiating invasive from noninvasive lesions [12, 13].

With these limitations in mind, most investigators now summarize the category 4 (high-grade intraepithelial neoplasia or high-grade dysplasia), category 5.1 (mucosal carcinoma or pT1a) and category 5.2 (submucosal carcinoma or pT1b) of the so-called Vienna classification [13] as "early Barrett's carcinoma" (Fig. 2). Although "watchful waiting" is still recommended by some investigators in patients with high-grade intraepithelial neoplasia/dysplasia in Barrett's esophagus (category 4) [15], most agree that these patients should be treated as patients with histologically proven mucosal or submucosal cancer (category 5). This is so because, based on surgical series, an occult invasive cancer is already present somewhere else in the Barrett mucosa in up to 50% of these patients [16]. Furthermore, even if an invasive cancer can be excluded by extensive biopsies and new endoscopic techniques, most of these patients will develop an invasive cancer within 5 years [17].

Prerequisites for a Limited Therapeutic Approach to Early Barrett's Cancer

Radical esophagectomy with extensive lymphadenectomy still constitutes the standard treatment for patients with early esophageal cancer [16, 18]. With this technique the 5-year survival rate approaches 90% [18–20]. This is, however, achieved at the price of substantial surgical mortality, morbidity, and a long-term compromise in the quality of life [21]. Consequently, the focus of recent studies has been the search for more limited procedures with lower mortality and morbidity and a better long-term functional result. These include limited surgical approaches [4, 22, 23] and a variety of purely endoscopic "organ-preserving" techniques—e.g., photodynamic therapy, laser ablation, mucosal destruction by argon beam plasma coagulation or electrocautery, endoscopic mucosal resection, and a combination of these [6–11].

A reduction of the radicality of the procedure in a patient with a potentially curable carcinoma, however, can be justified only if the chances for cure are not compromised. Complete macroscopic and microscopic tumor resection with an adequate safety margin (R0 resection) and removal of all potentially involved lymph nodes are the key factors for achieving cure in patients with gastrointestinal cancer [24]. Limiting the extent of the procedure thus requires an exact knowledge of the extent of the disease.

Our own experience and reports from other authors show that in about 50% of patients with early Barrett's cancer multicentric disease or multiple pre-neoplastic foci may be present throughout the Barrett mucosa [4, 25, 26] (Fig. 3). Removal of the entire area with intestinal metaplasia in the distal esophagus should therefore be considered mandatory in such patients to avoid recurrences.

Lymph node metastases or micrometastases were present in 13.1% of 129 patients who had resection for early Barrett's cancers at our institution. The relationship between depth of tumor infiltration and prevalence of lymph node metastases is shown in Table 1. Lymphatic spread could not be documented in any of the patients with high-grade intraepithelial neoplasia/dysplasia or carcinoma limited to the mucosa, whereas 22.4% of the patients with tumors infiltrating the submucosa had lymphatic spread. This is in marked contrast to early squamous cell cancer of the esophagus, which is more commonly associated with lymphatic spread (Table 1). The topographic analysis of the location of lymph node metastases showed that lymphatic spread in early Barrett's cancer follows certain rules. The most common location of lymph node metastases was the regional lymph node groups in the left and right paracardiac region, the lower posterior mediastinum, and the area along the left gastric artery (Fig. 4). More distant lymph node metastases in the tracheal bifurcation region, the proximal mediastinum, or at the celiac axis were uncommon and occurred only in patients with multiple positive regional nodes. A skipping of regional lymph node stations could not be observed.

Based on these observations, a simple destruction or endoscopic removal of the entire Barrett mucosa with preservation of the esophageal wall would, at least theoretically, be an attractive option in patients with high-grade neoplasia or cancer limited to the mucosa. However, none of the available imaging methods (including high-resolution endoscopic ultrasound probes, magnifying endoscopy, and chromoendoscopy) can differentiate high-grade neoplasia/mucosal carcinoma from submucosal cancer and exclude multicentric disease with a sufficient degree of accuracy. Even in patients who, based on pretherapeutic staging, have disease limited to the mucosa, a full-thickness resection of the entire segment with Barrett's esophagus and at least regional lymphadenectomy should be mandatory.

From a functional point of view, limited procedures should also be associated with a lower morbidity, mortality, and long-term side effects than esophagectomy, and should permit a better postoperative quality of life. The latter implies preservation of as much

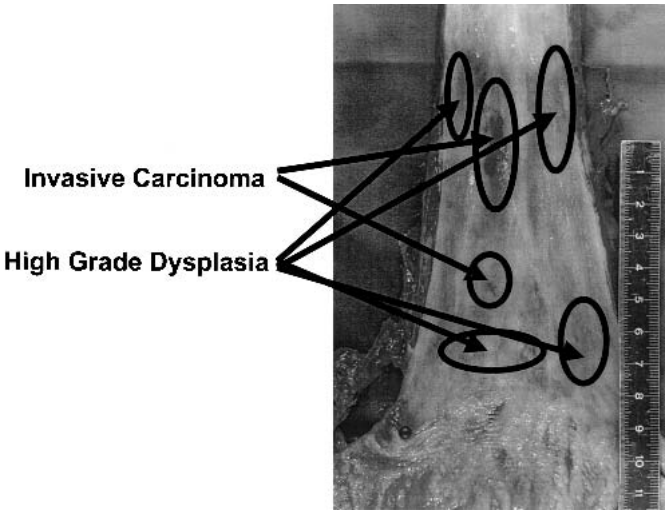

Fig. 3. A resection specimen with multiple foci of high-grade neoplasia and T1 cancer in long-segment Barrett's esophagus.

Table 1. Prevalence of lymph node metastases (including immunohistochemically proven micrometastases) in patients with resected squamous cell carcinoma and adenocarcinoma of the esophagus.

	Squamous cell cancer	Adenocarcinoma
HGN	0/6 (0%)	0/10 (0%)
pT1a	4/38 (10.5%)	0/43 (0%)
pT1b	35/87 (40.2%)	17/76 (22.4%)
Overall	39/131 (29.8%)	17/129 (13.1%)

HGN: high-grade neoplasia, according to the Vienna classification [13].

Data are from the Chirurgische Klinik und Poliklinik, Klinikum Rechts der Isar, Technische Universität München.

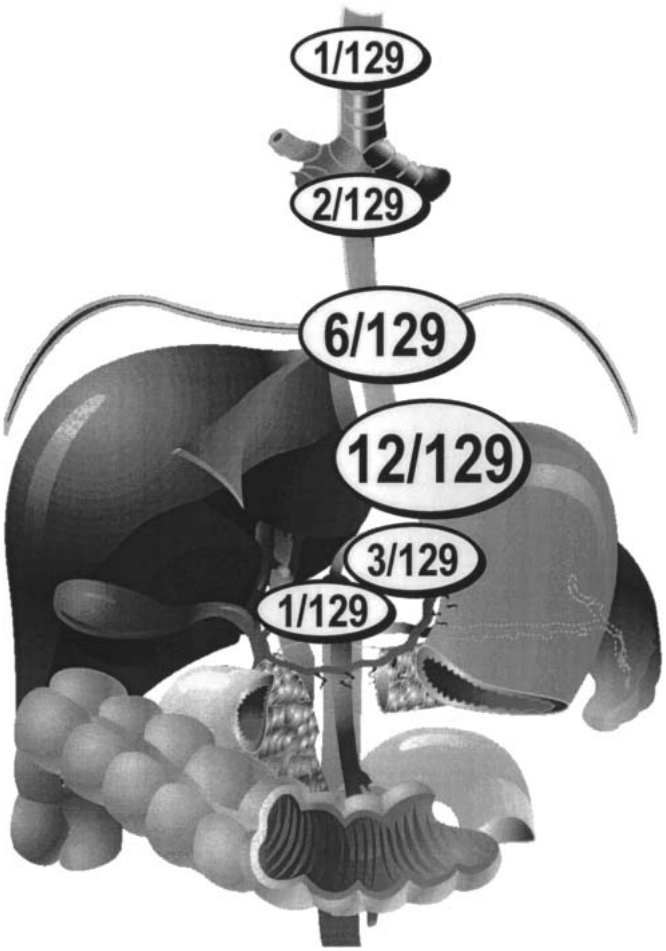

Fig. 4. Topographic anatomic distribution of lymph node metastases in 129 patients with resected early Barrett's cancer.

healthy esophagus and stomach as possible. Preventive aspects should also be taken into account. The precancerous nature of intestinal metaplasia in the distal esophagus argues for its complete removal once neoplasia has developed somewhere in the Barrett segment. Finally, because Barrett's esophagus and subsequent adenocarcinoma are a clear consequence of chronic gastroesophageal reflux, an intervention for early cancer should ideally also control the underlying reflux disease.

Taken together, these theoretical arguments and the principles of oncologic surgery indicate that complete full-thickness removal of the entire esophageal segment covered with Barrett's mucosa, in addition to regional lymphadenectomy, constitutes the minimal extent of resection for high-grade neoplasia as well as for mucosal and submucosal carcinoma in Barrett's esophagus. An antireflux procedure should be added to control for the underlying and usually severe gastroesophageal reflux disease.

Limited Surgical Resection for Early Barrett's Cancer

Based on the concepts presented here, we have adopted a limited surgical approach to early cancer [4]. Since July 1997 a total of 49 patients with high-grade neoplasia, mucosal cancer (T1a) or submucosal cancer (T1b) had a limited surgical resection of the distal esophagus and esophagogastric junction together with lymphadenectomy of the lower posterior mediastinum and upper abdominal compartment. The procedure was performed via a transabdominal approach and wide anterior splitting of the diaphragm [4]. Preservation of the vagal nerves was attempted whenever possible. To prevent postoperative reflux, reconstruction was performed with an interposed pedicled jejunal segment in a modification of the technique originally described by Merendino and Dillard (Fig. 5) [27].

Table 2 shows the results of limited resection in comparison to radical subtotal esophagectomy, the standard procedure for early Barrett's cancer at our institution before 1997. With both of these surgical approaches, complete tumor removal and removal of the entire segment with Barrett's mucosa was possible in virtually all patients. There was no significant difference in the median number of lymph nodes removed. Radical esophagectomy was, however, associated with a markedly higher postoperative morbidity and mortality. At postoperative follow up, 3/76 patients with radical esophagectomy developed recurrences, all three patients had a pT1b category and more than three positive lymph nodes. To date there have been no deaths or recurrences in patients who underwent limited resection. Survival analyses show no significant difference between the two procedures (Fig. 6) and no difference between patients with high-grade neoplasia / mucosal carcinoma and those with submucosal carcinoma (Fig. 7).

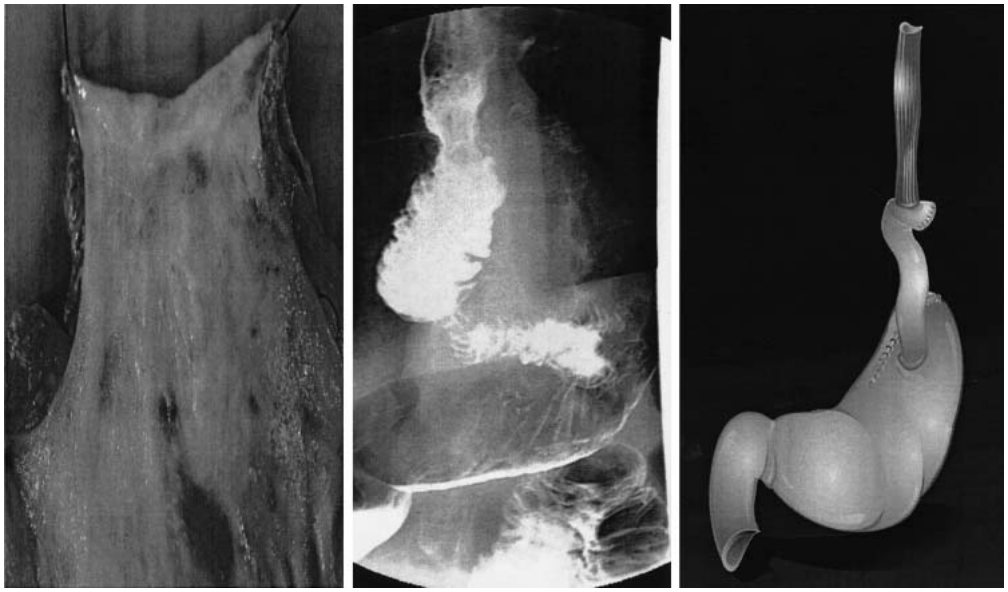

Fig. 5. Limited resection for early Barrett's cancer. Resection specimen (**left**), postoperative radiograph of jejunal interposition (**middle**), and schematic depiction of the procedure (**right**).

Table 2. Comparison of esophagectomy and limited surgical resection for patients with "early Barrett's carcinoma."

	Esophagectomy	"Limited resection"
Number	80	49
HGN/pT1a/pT1b	4/24/52	6/19/24
Complete tumor resection (R0-category)	80/80 (100%)	49/49 (100%)
Complete resection of Barrett muscosa	80/80 (100%)	47/49 (96%)
Median number of removed lymph nodes	22 (6–48)	19 (8–33)]
Morbidity	32/80 (40.0%)	7/49 (14.0%)
Postoperative mortality	3/80 (3.7%)	0/49 (0%)
Median F/U	78 months	41 months
Recurrences on F/U	3/76[a]	0/49

F/U: follow-up.

Data are from the Chirurgische Klinik und Poliklinik, Klinikum Rechts der Isar, Technische Universität München.

[a]All three patients with recurrences had three or more positive lymph nodes.

These results show that the above outlined oncologic goals in patients with early adenocarcinoma of the distal esophagus can be achieved by a limited surgical procedure. Radical subtotal esophagectomy is not necessary. The limited approach does not compromise the extent of lymphadenectomy in the lower posterior mediastinum and the upper abdominal compartment. A benefit of more extended lymphadenectomy in the upper mediastinum and cervical region in these patients is unlikely as, in our and others' experience [28, 29], lymph node metastases in the upper mediastinum or cervical region are indicators of advanced lymphatic spread and possible systemic spread, situations that cannot be cured even by radical surgery.

The potential for limited surgical resection in patients with early tumors of the distal esophagus or esophagogastric junction has recently also been recognized by several other authors [22, 23, 30]. A limited resection will, however, only be advantageous for the patient if, in addition to a reduced morbidity and mortality, it is combined with a reconstructive procedure providing optimal alimentary function and prevention of gastroesophageal reflux. The options for reconstruction after limited resection include esophagogastrostomy, colon interposition, and interposition of a pedicled jejunal segment. Esophagogastrostomy has been plagued by poor functional results with severe reflux after resection of the lower esophageal sphincter. Colon interposition is associated with high morbidity and mortality.

The concept of an interposed jejunal segment as a substitute for the lower esophageal sphincter was experimentally tested and clinically introduced by Merendino and Dillard in 1955 as an antireflux procedure [27]. They showed that after resection of the esophagogastric junction interposition of a 15-cm segment of isoperistaltic jejunum behaves like a physiological sphincter and protects against gastroesophageal reflux. The use of mechanical staplers for the esophagojejunal anastomosis has made this procedure simple and safe. Low morbidity and mortality, in combination with excellent long-term functional results for this procedure, were recently reported by several investigators in the treatment of undilatable or recurrent distal esophageal strictures and other benign lesions that required resection of the distal esophagus and cardia [31, 32]. Histologic studies of endoscopic biopsies of the interposed jejunal loops confirmed the retention of a normal villous architecture with Paneth cell hyperplasia but no evidence of metaplasia or dysplasia at long-term follow up [33, 34]. The follow-up of our patients with limited resection and jejunum interposition showed that 84% were asymptomatic; furthermore, 88% had no evidence of esophagitis on endoscopy. Of 35 patients with a follow-up of more than 1 year, 86% have regained their preoperative weight. A postoperative structured quality of life assessment using the "Gastrointestinal Quality of Life Index" [35] showed no overall difference in a comparison with a normal population. The major postoperative problems were gastric emptying disorders in four patients and distension of the interposed jejunal loop caused by anastomotic stricture in two patients. Gastric emptying disturbances may be further reduced by careful vagal preservation [23]. Interposition of an isoperistaltic jejunal segment after limited resection of the distal esophagus thus overcomes most of the disadvantages of other reconstruction methods.

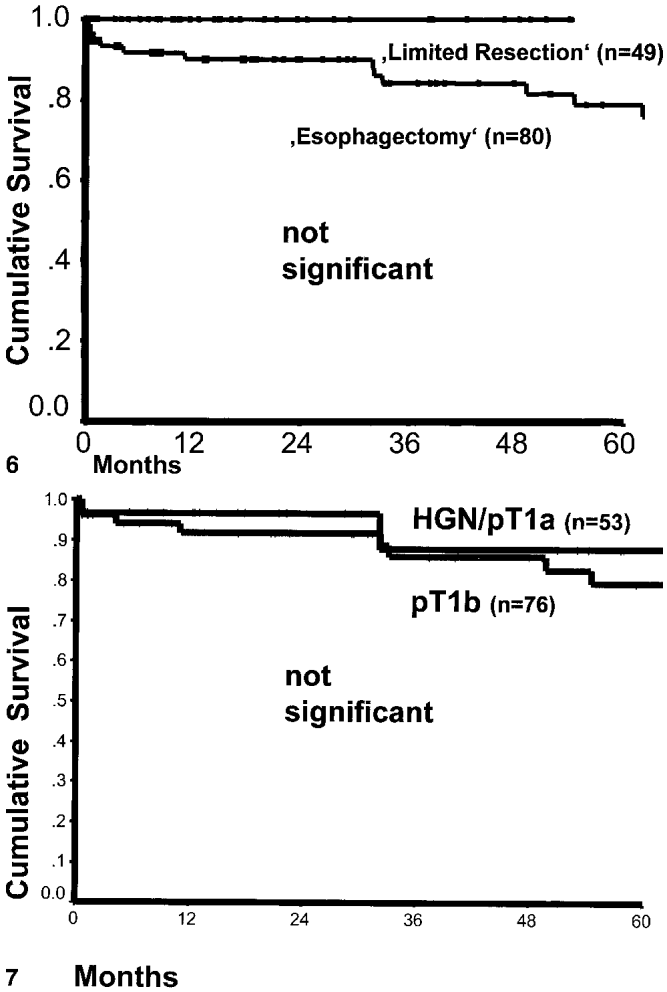

Fig. 6. Kaplan-Meier survival curves after radical esophagectomy and limited resection for early Barrett's cancer.

Fig. 7. Kaplan-Meier survival curves for high-grade neoplasia (HGN)/mucosal cancer (pT1a), and submucosal (pT1b) cancer after surgical resection.

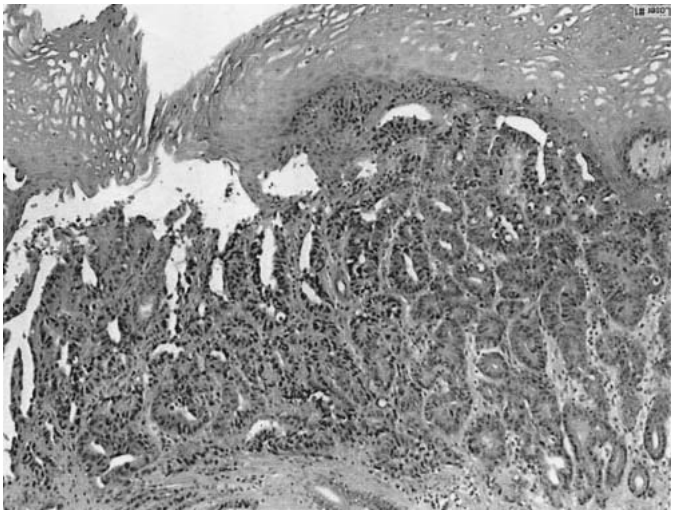

Fig. 8. Persistence of intestinal metaplasia and dysplasia under squamous epithelium after endoscopic ablation of early esophageal adenocarcinoma.

Endoscopic Ablation, Endoscopic Resection

Compared to limited surgical procedures, endoscopic ablation or mucosal resection techniques for early Barrett's cancer are even less invasive and also offer the appealing advantage of complete "organ preservation." A major disadvantage of these techniques is, however, that they completely disregard the problem of multicentricity and lymph node metastases.

An analysis of the results of endoscopic ablation is difficult, because the techniques do not yield a resection specimen for histopathologic assessment. Therefore, the true extent of the disease and tissue destruction cannot be assessed objectively. In addition, aggressive ablation therapy has been reported to result in esophageal perforations and a high rate of strictures. Consequently the use of these techniques in patients with early Barrett's cancer is now discouraged by most professional organizations.

Endoscopic mucosal resection is increasingly replacing endoscopic mucosal ablation in many centers [6, 10]. In contrast to ablation, the results of endoscopic mucosal resection can be objectively compared to surgical resection. In the largest published series on endoscopic mucosal resection for early Barrett's cancer the complication rate was comparable to limited surgical resection, whereas tumor recurrences and/or metachronous lesions at follow-up were markedly more frequent. May et al. report metachronous / recurrent cancers within the Barrett mucosa in 30% of their patients after a mean follow-up of only 34 months [36]. Although those authors argue that the lesions can easily be addressed again by endoscopic intervention, this high recurrence rate in patients with curable tumors casts serious doubt on the oncologic adequacy of the endoscopic procedure.

Recurrent or metachronous lesions after mucosal resection are due to incomplete removal of the Barrett's mucosa when performing mucosectomy. A combination of mucosal resection and thermal or photodynamic ablation of persistent Barrett's mucosa is therefore now used to eliminate the risk of recurrences. However, even after apparent macroscopic complete ablation of Barrett's esophagus, islands with intestinal metaplasia often persist under squamous re-epithelialization of the distal esophagus (Fig. 8). Adenocarcinoma can still develop in these areas, but it is now hidden from endoscopic view, making surveillance impossible and depriving the patients of the chance for early detection and cure of Barrett's cancer. A series of such patients have already been seen at our institution. In addition a combination of mucosal resection with ablative techniques has been reported to result in an esophageal stricture rate as high as 30% [37].

Because neither ablation nor endoscopic mucosal resection adequately addresses the underlying reflux problem of these patients, continuous high-dose acid suppression is considered mandatory after all forms of endoscopic intervention. Although quality of life data are so far not available after endoscopic therapy of early Barrett's cancer, persistent reflux and a high tumor recurrence rate are likely to have a negative effect.

Summary

Advantages and disadvantages of the available treatment alternatives for early Barrett's cancer are summarized schematically in Table 3. The major disadvantages of the current standard—i.e.,

Table 3. Summary of the major advantages and disadvantages of current treatment options for early Barrett's cancer.

	Radical resection	Limited resection	Endoscopic mucosectomy
R0 resection	+++	+++	+
Lymphadenectomy	+++	++	−−−
Low invasiveness	−−−	−	++
Low morbidity/mortality	−−	+	+
Prevent recurrences	+++	+++	−−
Removal of precursor	+++	+++	−
Prevention of reflux	−	++	−−−
Good quality of life	−−	++	???

+++: Very effective; −−−: very ineffective.

radical esophagectomy and lymphadenectomy—are its invasiveness, associated morbidity and mortality, and the poor postoperative quality of life. These disadvantages can be overcome by limited resection, regional lymphadenectomy, and jejunal interposition. Our experience with limited surgical resection indicates that it is safer than esophagectomy, and it is oncologically adequate. Furthermore, it prevents gastroesophageal reflux and is associated with good quality of life. In contrast, the value of endoscopic mucosal resection, although theoretically attractive as a very little invasive procedure, is compromised by the lack of lymphadenectomy, frequent persistence of Barrett's esophagus, high rate of recurrences and/or metachronous lesions, and the continued need for medical acid suppression and surveillance. A direct comparison of limited surgical resection with endoscopic mucosectomy, ideally in a randomized fashion, is, however, required before one or the other of the limited approaches can be considered as standard for patients with early Barrett's carcinoma. Nonetheless, radical total or subtotal esophagectomy with extensive lymphadenectomy certainly appears to be too aggressive for these early tumors.

Both endoscopic mucosal resection techniques and transabdominal limited surgical resection reach their limits in patients with long segments of intestinal metaplasia in the esophagus. Esophageal stripping with vagal nerve preservation, as suggested by Akiyama et al. [38] and Banki et al. [23], or limited resection of the esophageal segment covered by metaplastic epithelium through a combined transabdominal and transthoracic approach with jejunal interposition may constitute an alternative to subtotal esophagectomy in these patients.

Résumé. On fait le diagnostic d'adénocarcinome de l'oesophage distal de plus en plus souvent à un stade précoce en raison des programmes de surveillance efficaces chez les patients porteurs d'oesophage de Barrett connu. Avec l'introduction des modalités thérapeutiques chirurgicales et endoscopiques moins invasives, la nécessité de pratiquer une oesophagectomie radicale avec lymphadénectomie étendue chez ces patients a été remise en cause. Quand on choisit une approche au cancer de Barrett au début, on doit prendre en compte la nature précancéreuse de l'oesophage de Barrett sous-jacent, la multicentricité fréquente des altérations néoplasiques à l'intérieur de la muqueuse de Barrett, l'inexactitude des modalités de staging, la présence de métastases ganglionnaires, mais aussi le caractère invasif et la morbidité en rapport avec ces procédés tout comme les aspects de qualité de vie. D'un point de vue oncologique, l'étendue minimale de la résection pour cancer de Barrett au début doit inclure l'ablation de toute l'épaisseur de l'oesophage distal siège de la métaplasie intestinale et un curage ganglionnaire régional. Chez des patients sélectionnés, la résection peut être réalisée par des procédés limités à type de résection transhiatale de l'oesophage distal, mais nous ne préconisons ni l'ablation ni la résection endoscopique de la muqueuse. Nous rapportons ici notre expérience de 49 résections chirurgicales limitées avec lymphadénectomie régionale dont les résultats nous permettent d'affirmer que le procédé est sur et oncologiquement suffisante. La reconstruction avec une anse intestinale interposée prévient le reflux gastro-oesophagien postopératoire et est associé à un bon niveau de qualité de vie. En revanche, les interventions endoscopiques sont frappées d'un taux prohibitif de récidive, probablement par persistance de muqueuse de Barrett et le reflux gastro oesophagien.

Resumen. Debido a la eficacia de los programas de vigilancia en pacientes diagnosticados de esófago de Barrett, el adenocarcinoma distal de esófago se detecta, frecuentemente, en estadios precoces. Desde la introducción del tratamiento endoscópico y de la cirugía limitada, la necesidad de esofagectomías radicales con extensas linfadenectomias es dudosa. Para decidir el tratamiento de un esófago de Barrett hay que tener en cuenta diversos hechos: la naturaleza precancerosa subyacente al esófago de Barrett, la frecuente muticentricidad de las alteraciones neoplásicas en la mucosa de Barrett, la inexactitud de las actuales modalidades de estadificación y, la presencia de adenopatías metastásicas. También han de considerarse otros aspectos: la capacidad invasiva, la morbilidad del tratamiento y como éste puede afectar a la calidad de vida del paciente. Desde el puntos de vista oncológico la resección mínima en un cáncer precoz de Barrett ha de comprender la totalidad del segmento distal del esófago recubierto por la metaplasia, junto con los ganglios regionales (linfadenectomia regional). En pacientes seleccionados esto puede conseguirse mediante una resección limitada transhiatal del esófago distal, pero en modo alguno mediante ablación o resección endoscópica de la mucosa. Nuestra experiencia basada en 49 esofagectomías limitadas con linfadenectomía regional, muestra que este es un procedimiento seguro y oncológicamente adecuado. La reconstrucción con asa yeyunal interpuesta previene el reflujo gastro-esofágico y proporciona una buena calidad de vida. Por el contrario, intervenciones endoscópicas originan una elevada tasa de recidivas debidas, probablemente a la persistencia de mucosa de Barrett y al reflujo gastro-esofágico.

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