Today's Mistakes and Tomorrow's Wisdom in the Surgical Treatment of Barrett's Adenocarcinoma

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Abstracts

Background: Barrett's esophagus is a premalignant condition caused by longstanding gastroesophageal reflux disease and may progress to low-grade dysplasia, high-grade dysplasia (HGD), and finally esophageal adenocarcinoma. ***Summary:*** Barrett's adenocarcinoma can be treated either by endoscopic or surgical resection, depending on the clinical staging. Endoscopic resection is a safe and adequate treatment option for HGD, mucosal tumors, and low-risk submucosal tumors. Its role in the treatment of high-risk submucosal tumors and the role of organ-preserving sentinel node navigated surgery are still under investigation. Esophagectomy with neoadjuvant chemoradiation or perioperative chemotherapy is considered the standard of care for locally advanced Barrett's adenocarcinoma. Regarding operative technique, there is no proven superiority of one technique over another, although a minimally invasive transthoracic technique seems most commonly applied nowadays. In this review, state-of-the-art evidence and future expectations are presented regarding indications for resection, neoadjuvant or perioperative therapy, type of surgery, and postoperative follow-up for Barrett's adenocarcinoma. ***Key Messages:*** In Barrett's adenocarcinoma, endoscopic resection is the standard treatment option for low-risk mucosal and submucosal tumors. For high-risk submucosal tumors, endoscopic submucosal dissection with close surveillance and sentinel node navigated surgery are currently being studied. For locally advanced cancer, a multimodal therapy including esophagectomy is the standard of care. Nowadays, in high-volume centers, a minimally invasive transthoracic esophagectomy with an intrathoracic anastomosis is the most common procedure for Barrett's adenocarcinoma.

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Introduction

Barrett's esophagus is defined as a metaplastic change in the squamous lining of the distal esophagus, with replacement of squamous by columnar epithelium [1]. It is a premalignant condition caused by longstanding gastroesophageal reflux disease, which may progress to low-grade dysplasia, high-grade dysplasia (HGD), and in less than one per cent of patients, esophageal adenocarcinoma (EAC) [2]. Surveillance and treatment of Barrett's esophagus lie mainly with the gastroenterologist, but it is named after a surgeon: the Australian Norman Rupert Barrett [3]. He believed that it was caused by shortening of the esophagus, which pulled up the stomach above the diaphragm. When cancer develops in Barrett's esophagus, treatment generally consists of resection. So, this is the stage of the condition where the contemporary surgeon is still predominantly involved. This review aims to provide an overview of the present evidence and thus identify today's mistakes and tomorrow's wisdom, on the surgical treatment of Barrett's adenocarcinoma.

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Table 1. Risk of LNM and recommended treatment of mucosal and submucosal tumors

	Risk of LNM, %	Recommended treatment
HGD/mucosal (T1a)	~1	EMR/ESD
HGD/mucosal (T1a) with high-risk features[1]	Not known	EMR/ESD
Submucosal (T1b), low risk[2]	≤2	ESD
Submucosal (T1b), high risk[3]	16–44[4]	Surgical resection

[1] Lymphovascular invasion or poor differentiation. [2] ≤500 μm with no histopathologic risk factors. [3] >500 μm or with poor differentiation, lymphovascular invasion, or after non-radical resection. [4] Actual incidence of LNM may be lower; ESD with endoscopic follow-up may be a valid alternative treatment (results of the PREFER study are awaited).

Endoscopic or Surgical Resection

"A surgeon is a doctor who can operate and knows when not to," is a famous quote attributed to legendary Swiss surgeon Theodor Kocher (1841–1917). This may well be applied to early Barrett's adenocarcinoma. When deciding whether to operate on early Barrett's adenocarcinoma or not, one has to weigh up the morbidity and mortality of an esophagectomy on one side and the oncological risk of endoscopic resection and leaving the esophagus and locoregional lymph nodes in situ on the other side Table 1.

The oncological risk of organ-preserving treatment is generally represented by the risk of lymph node metastasis (LNM). HGD or mucosal tumors carry a risk of lymph node involvement of around 1% [4, 5]. Endoscopic resection, either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), has been shown to be safe and adequate with excellent long-term remission, and therefore, it is the first choice of treatment [4]. However, it must be noted that in the case of high-risk features, such as lymphovascular invasion or poor differentiation, the exact risk of LNM is unknown [6].

For cancers invading the submucosa, a distinction is made between low and high risk of LNM. Superficially invading tumors (i.e., ≤500 μm) with no histopathologic risk factors for LNM that are removed radically by endoscopy have a risk of LNM below 2% [7, 8]. Since this is under the reported 30-day mortality of esophagectomy in large international series, endoscopic resection with follow-up is a valid treatment option in these patients [9].

Tumors invading deeper than 500 μm, or with poor differentiation, lymphovascular invasion, or after nonradical resection, are considered as high-risk for lymph node involvement, with percentages varying from 16 to 44%, based on surgical series [10, 11]. The risk of LNM may actually be lower, as shown in recent series on LNM in high-risk submucosal cancers that were treated endoscopically [12, 13]. Increasing experience with the technique and follow-up of endoscopic resection has led to a gradual shift toward more endoscopic treatment in submucosal cancers. The largest series up-to-date of ESDs for early EAC, includes 130 completed ESDs, of which 67 were for submucosal cancers. The combined en-bloc/R0 rates were 87% for HGD or T1a tumors and 49% for T1b tumors. After R1-resection, only 29% of patients actually had a residual tumor; all were detected at first follow-up endoscopy. The rate of LNM in the operated patients was low. The results suggest that follow-up with endoscopy 8 to 12 weeks after ESD may help to detect patients who are truly R1, i.e., who indeed have residual tumor and may therefore benefit from additional esophagectomy. Furthermore, follow-up endoscopy may also reveal patients who actually have T2 tumors and may therefore benefit from neoadjuvant therapy instead of upfront surgery. Regarding the risk of LNM of submucosal tumors, the results of the PREFER study (ClinicalTrials.gov NCT03222635), which will prospectively investigate the feasibility and safety of endoscopic follow-up after endoscopic resection of submucosal EAC, may provide tomorrow's wisdom and tell if today we operate too much for early Barrett's EAC.

The intraluminal recurrence rate after endoscopic resection varies from 14.5% for HGD and mucosal tumors to 33% for high-risk submucosal tumors. However, the success rate of repeat endoscopic treatment (66–100%) is reassuring [4–8, 11, 12].

Sentinel Node Navigated Surgery

Sentinel node navigated surgery may be another alternative to esophagectomy in high-risk T1b tumors. Lymph node dissection may then be performed without resection of the esophagus. This has been shown to be feasible in human cadavers, with a high technical success rate and without signs of vascular compromise in a porcine model [14]. Sentinel node identification is feasible with high accuracy, with Technetium-99m and indocyanine green [15]. In a pilot study in esophagectomy patients however in whom the operation was started with a thoracolaparoscopic dissection of all areas involving drainage of the esophagus, there were signs of discoloration of the esoph-

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agus at the end of the lymph node dissection, possibly indicating ischemia [16]. Future studies, such as the SNAP III study (Netherlands Trial Register NL8100), must provide tomorrow's wisdom and tell whether sentinel node navigated surgery, with focused resection of the sentinel lymph node stations and preservation of the esophagus, is a feasible and safe alternative to esophagectomy in high-risk cT1bN0 patients.

Neoadjuvant Therapies

For locally advanced esophageal carcinoma, i.e., cT2 or higher or cN+, the concept of neoadjuvant or perioperative therapy has been rapidly emerging in recent decades.

Neoadjuvant Chemotherapy

Since the late 1980s, several studies showed that neoadjuvant chemotherapy with cisplatin improved overall survival of patients with locally advanced esophagogastric cancer [17–19]. The long-term outcomes of the OEO2 and RTOG trials were conflicting concerning the survival benefit of neoadjuvant treatment [20, 21]. However, the OEO2 results, showing a survival benefit for two cycles of cisplatin and fluorouracil before surgery, can be considered more representative for Barrett's adenocarcinoma as 66.5% of the included patients had EAC, and 64% of the tumors were located in the distal esophagus.

The concept of perioperative chemotherapy emerged as a therapeutic alternative to neoadjuvant treatment and surgery alone for patients with esophagogastric cancer [22, 23]. The MAGIC trial demonstrated that perioperative epirubicin, cisplatin, and fluorouracil (ECF) significantly improves survival in patients with gastric or lower EAC [24]. However, most of the enrolled patients (74%) had gastric cancer. In the FLOT4-AIO trial, showing a significantly better survival of perioperative fluorouracil plus leucovorin, oxaliplatin, and docetaxel compared to ECF, 66% of patients had a junction tumor [25]. Nowadays, FLOT is the most applied perioperative chemotherapy regimen for distal esophagus and GEJ adenocarcinoma in Western countries [26–28].

Neoadjuvant Chemoradiotherapy

The first randomized trials investigating neoadjuvant chemoradiation (CRT) for esophageal and GEJ adenocarcinoma are dated in the 1990s, and their results were contradictory [29, 30]. In 2006, the results of a phase II study of neoadjuvant CRT with weekly paclitaxel and carboplatin for esophageal cancer were published: 100% R0 resection, 25% complete pathological response, and 36.5% of patients had less than 10% vital residual tumor cells [31]. These promising results were the rationale for

the subsequent multicenter, randomized, CROSS-trial [32]. Patients with resectable esophageal tumors were randomized to surgery alone or 5 weeks of neoadjuvant CRT (carboplatin and paclitaxel with concurrent radiotherapy) followed by surgery. Most of the enrolled patients had EAC (75%). Even though subgroup analyses revealed that squamous-cell carcinoma was more sensitive to CRT than EAC, survival in EAC patients was better in the CRT group, with a median overall survival of 43.2 months in the CRT group, versus 27.1 months in the surgery alone group [32]. Additional analyses demonstrated lower locoregional recurrence (34% vs. 14%) and peritoneal carcinomatosis (14% vs. 4%) in the CRT group [33]. Considering the results of this landmark trial, CRT is currently the gold standard for locally advanced esophageal and GEJ cancer in many Western countries [27, 34].

Chemotherapy versus Chemoradiotherapy

The choice between perioperative chemotherapy and neoadjuvant CRT for esophageal and GEJ adenocarcinoma is a hot topic in the current scientific debate. Several multicenter European studies compared peri-/preoperative chemotherapy (ECF, ECX, or FLOT regimen) plus surgery to CRT plus surgery (CROSS regimen) [35–37]. None of these studies demonstrated a survival benefit of one treatment option compared to the other. Anderegg et al. [35] concluded that neoadjuvant CRT should be considered as a first choice protocol because of a lower incidence of severe adverse events.

So far the long-term results of the two randomized trials, POET and NeoRes I, did not show any survival benefit of preoperative CRT over chemotherapy [38, 39]. Nonetheless, the POET trial results revealed a significantly improved 5-year progression-free survival in the CRT group [38]. Furthermore, in chemotherapy patients, disease-free survival and recurrence rates are significantly better after a higher lymph node yield, whereas in CRT, the extent of lymphadenectomy seems less important for locoregional control [36].

Several trials are expected to provide more "tomorrow's wisdom" with regard to the best neoadjuvant or perioperative therapy in EAC. The interim results of the TOPGEAR trial and the preliminary data of the Neo-AEGIS trial showed that preoperative CRT can be safely delivered and that there is still no evidence that perioperative chemotherapy is unacceptably inferior to the CROSS regimen [40, 41]. Regarding Barrett's adenocarcinoma specifically, these trials have some limitations. In the TOPGEAR trial, only 27% of patients had GEJ cancer. The Neo-AEGIS chemotherapy arm has enrolled patients treated with modified MAGIC regimens until 2018 and FLOT regimen afterward. Considering the superiority of FLOT, this could result in an underestimation of the che-

motherapy effect. To overcome this limitation, the ESO-PEC trial aims to compare two actual standard of care treatments: CROSS versus FLOT for esophageal and junctional adenocarcinoma [42].

Type of Surgery

Type of Resection

Surgery has played a central role in Barrett's adenocarcinoma since long [43–46]. In 1990, DeMeester et al. [44] concluded that "the extent of resection should be adapted to the extent of disease present." Interestingly, this does not differ from the recommendations in the current British and American guidelines for the surgical management of Barrett's adenocarcinoma [1, 47]. Indeed esophagectomy is recommended in case of invasion to the mid- or deep submucosa (T1b, sm2–3) or after endoscopic resection of a T1a or T1b sm1 adenocarcinoma with negative prognostic features and for ≥T2 tumors or N+ disease, with consideration of neoadjuvant therapy for the latter categories [1, 47].

The historical debate in surgery for Barrett's adenocarcinoma used to be centered around two surgical approaches: transhiatal (THE) and transthoracic esophagectomy (TTE). Supporters of THE argue that the primary direction of lymphatic metastatic spread from the distal esophagus is the lymphatic basin around the celiac axis, together with the lower posterior mediastinum and the paracardial region [48–50]. Based on that hypothesis, they claim that a radical THE with en bloc lymphadenectomy of these lymphatic stations is oncologically adequate. On the other hand, TTE allows for an extended lymph node dissection in the posterior middle and upper mediastinum, aiming to decrease locoregional recurrence and improve pathological staging [46, 51].

Nowadays, evidence concerning survival benefit supporting one technique of esophagectomy over another is still lacking [52–56]. The main common findings of the published series and a Dutch RCT were lower morbidity for THE and an increased number of harvested lymph nodes for TTE. Nonetheless, the long-term results of the aforementioned randomized trial showed that the subgroup of patients with a limited number (1 to 8) of positive lymph nodes, undergoing TTE, had a significant advantage in 5-year disease-free survival [55].

The extent of lymphadenectomy is considered an important factor in the choice of the surgical approach for Barrett's adenocarcinoma, even if the exact LNM distribution pattern is still unknown [57, 58]. Middle thoracic paraesophageal LNMs are present in up to 25% of patients with GEJ adenocarcinoma undergoing upfront surgery [59]. Even after neoadjuvant CRT, supracarinal positive lymph nodes have been described in up to 14% per lymph node station [36, 58]. This may be an argument for a transthoracic approach. A recent international survey conducted among experienced esophageal surgeons, highlighted that there is no standardized strategy for the extent of lymphadenectomy [60]. The results of the multinational observational TIGER study will provide tomorrow's wisdom with regards to the distribution of LNM in esophageal cancer [61].

Minimally Invasive Approach

Between 2011 and 2012, three European RCTs comparing minimally invasive to open esophagectomy were registered: the TIME trial (thoracolaparoscopic vs. open), the MIRO trial (hybrid vs. open), and the ROBOT trial (robotic-assisted vs. open) [62–64]. The short-term results of the Dutch TIME trial, namely less pulmonary complications, shorter hospital stay, and a better short-term quality of life (QoL), led to the gradual implementation of minimally invasive esophagectomy (MIE) in the Netherlands [65, 66]. Recently, a study from the Dutch audit, with 3,135 patients undergoing esophagectomy from 2016 to 2019, showed that 90% of patients were treated by MIE [67]. Most patients had EAC (79.1%) and underwent TTE (81.6%). However, MIE has not reached a worldwide distribution yet. An international survey with respondents from 49 different countries and 6 different continents pointed out that the minimally invasive approach for esophagectomy raised from 14% in 2007 to 43% in 2014 [68, 69]. The Esophageal Complications Consensus Group (ECCG) involving 24 high-volume esophageal surgical centers in 14 countries reported a MIE rate of 47.9% between 2015 and 2016 [9]. A recent update of the same group, including data from 15 additional high-volume international esophagectomy centers, revealed that minimally invasive surgery surpassed the open approach for esophagectomy: 52.8% versus 47.2%. Moreover, a comparison between two different periods of the study, 2015–2016 versus 2017–2018, showed a significant increase of MIE (48.0% vs. 56.7%, $p < 0.001$) [70]. Nowadays, the long-term outcomes of all the aforementioned RCTs support MIE [71–73]. Nonetheless, in order to maintain favorable postoperative morbidity rates, it is recommended to perform MIE in high-volume centers [67, 74].

With increasing use of TTE and MIE, more and more centers shifted toward an intrathoracic anastomosis (Ivor Lewis esophagectomy). However, there was a lack of evidence on the preferred location of the anastomosis after TTE. Recently, the results of a Dutch multicenter randomized clinical superiority trial (ICAN), showed that patients with intrathoracic anastomosis had lower anastomotic leak rates, fewer severe complications, lower recurrent laryngeal nerve palsy, and better QoL compared to those with a cervical anastomosis [75].

Regarding robotic-assisted MIE (RAMIE), two meta-analyses showed some benefits for the RAMIE, in terms of blood loss, vocal cord palsy, pneumonia, morbidity, and R0 resection rate [76, 77]. The short-term results of the ROBOT-2 trial, comparing RAMIE to MIE Ivor Lewis, are awaited in 2023 and will provide more wisdom regarding the benefits of robotic-assisted surgery [78]. Meanwhile, several authors reported a shorter learning curve for RAMIE (20–40 cases) compared to standard MIE (25–175 cases), especially with a structured proctored training pathway [79–83]. The efficacy of lymphadenectomy is considered an essential indicator of the learning curve progress, in the international consensus statement on RAMIE [84].

The most common recommendation about surgical approach for esophagectomy for Barrett' adenocarcinoma is that the procedure must be tailored according to patient's characteristics, including at least a two-field lymphadenectomy, and should be performed in a high-volume center setting. Esophageal cancer surgery in high-volume hospitals is associated with better short- and long-term outcomes compared to low-volume centers [67, 74, 85–87]. These findings have been the main reason for the centralization of esophageal surgery and the founding of national clinical registries. In the Netherlands, a volume standard of 10 esophagectomies per year was introduced in 2006, and it was raised to 20 in 2011. A recent study from the Dutch Upper Gastrointestinal Cancer Audit reported a volume outcome trend that plateaued at 50–60 annual resections for most outcomes, but lymph node yield and anastomotic leakage continued to improve with increasing volume [67].

Finally, concerning postoperative QoL, there is a general agreement in favor of both MIE and RAMIE for the domains "global QoL," "physical functioning," "fatigue," and "pain" [88–90]. However, it is still controversial if those advantages remains significant during long-term follow-up [66, 90–95]. Surprisingly, QoL of patients undergoing esophagectomy is restored to baseline level in 12 months, irrespective of the occurrence of postoperative complications such as anastomotic leakage [96]. Evidence comparing MIE and RAMIE with regards to QoL is still lacking. The results of the ROBOT-2 trial may shed some light on this topic [78].

Follow-Up after Surgery
Barrett's type metaplasia after esophagectomy was first described in the 1970s; chronic reflux of both acid and bile has been identified as the main underlying etiology [97, 98]. The prevalence of Barrett's metaplasia on the esophageal stump can vary, depending on the definition, from 17% for specialized intestinal metaplasia (columnar epithelium with goblet cells) to 38% for the presence of columnar metaplasia of any type [99].

In the literature there is agreement about an increase of esophagitis and Barrett's metaplasia in the esophageal stump over time [100–102]. Predisposing factors for metaplasia include a preoperative diagnosis of adenocarcinoma or Barrett's esophagus, an anastomosis below the level of the azygos vein, and a pylorus drainage procedure, such as pyloroplasty [101, 103, 104].

The optimal duration of endoscopic follow-up after esophagectomy has not been determined yet. Several long-term follow-up results suggest extending the endoscopic surveillance beyond 5 years [100, 102]. However a recent study, including 619 patients undergoing Ivor Lewis esophagectomy for EAC, showed a low incidence of both intestinal metaplasia (2%) and local adenocarcinoma recurrence (6%) in the esophageal stump [105]. The authors, in accordance with the British guidelines, recommend a post-esophagectomy endoscopic surveillance only on a symptomatic basis [1, 105]. The ENSURE study (ClinicalTrials.gov NCT03461341), a multicenter observational study on surveillance after esophagectomy, is expected to provide more "tomorrow's wisdom" regarding the optimal postoperative surveillance protocol after resection of Barrett's adenocarcinoma.

Conclusion

Barrett's adenocarcinoma should be resected when possible. Endoscopic resection can be applied to low-risk mucosal and submucosal tumors; however, endoscopic resection with close surveillance and sentinel node navigating surgery may be valid organ-sparing alternatives to esophagectomy in high-risk T1b tumors but are still limited to trial setting. cT2 or higher tumors or locoregional cN+ disease should be treated with multimodal therapy including esophagectomy. Esophagectomy for Barrett's adenocarcinoma nowadays mostly is performed by minimally invasive TTE, with an intrathoracic anastomosis; however, it is recommended to use the technique that one is most familiar with, in the setting of a high-volume center.

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