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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.

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 nonradical 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-

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 ESOPEC 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.

Conflict of Interest Statement

Mark Ivo van Berge Henegouwen is a consultant for Mylan, Alesi Surgical, Medtronic, and Johnson and Johnson and has received research grants from Olympus and Stryker, paid to the institute. Giovanni Maria Garbarino, Suzanne S. Gisbertz, and Wietse J. Eshuis have no conflicts of interest to declare.

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Author Contributions

Giovanni Maria Garbarino: literature search and drafting the manuscript; Mark Ivo van Berge Henegouwen and Suzanne S. Gisbertz: study conception and design and critical revision of the manuscript; Wietse J. Eshuis: literature search, study conception and design, drafting the manuscript, and critical revision of the manuscript. All the authors have approved this paper.

References

1 Fitzgerald RC, Di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014;63(1):7–42.
2 Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011 Oct 13;365(15):1375–83.
3 Barrett NR. Chronic peptic ulcer of the oesophagus and "oesophagitis". Br J Surg. 1950;38(150):175–82.
4 Pech O, May A, Manner H, Behrens A, Pohl J, Weferling M, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology. 2014 Mar;146(3):652–60.e1.
5 Alvarez Herrero L, Pouw RE, Van Vilsteren FGI, Ten Kate FJW, Visser M, Van Berge Henegouwen MI, et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy. 2010;42(12):1030–6.
6 Nieuwenhuis EA, Pech O, Bergman JJGHM, Pouw RE. Role of endoscopic mucosal resection and endoscopic submucosal dissection in the management of Barrett's related neoplasia. Gastrointest Endosc Clin N Am. 2021 Jan 1;31(1):171–82.
7 Manner H, May A, Pech O, Gossner L, Rabenstein T, Günter E, et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol. 2008 Oct;103(10):2589–97.
8 Schölvinck D, Künzli H, Meijer S, Seldenrijk K, van Berge Henegouwen M, Bergman J, et al. Management of patients with T1b esophageal adenocarcinoma: a Retrospective Cohort Study on patient management and risk of metastatic disease. Surg Endosc. 2016 Sep 1;30(9):4102–13.
9 Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G, et al. Benchmarking complications associated with esophagectomy. Ann Surg. 2019 Feb 1;269(2):291–8.
10 Buskens CJ, Westerterp M, Lagarde SM, Bergman JJ, Ten Kate FJ, Van Lanschot JJ. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc. 2004;60(5):703–10.
11 Westerterp M, Koppert LB, Buskens CJ, Tilanus HW, Ten Kate FJW, Bergman JJHGM, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch. 2005 May;446(5):497–504.
12 Manner H, Pech O, Heldmann Y, May A, Pauthner M, Lorenz D, et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc. 2015 Jul 19;29(7):1888–96.
13 Künzli HT, Belghazi K, Pouw RE, Meijer SL, Seldenrijk CA, Weusten B, et al. Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma. United Eur Gastroenterol J. 2018 Jun 1;6(5):669–77.
14 Künzli HT, van Berge Henegouwen M, Gisbertz S, Seldenrijk C, Kuijpers K, Bergman J, et al. Thoracolaparoscopic dissection of esophageal lymph nodes without esophagectomy is feasible in human cadavers and safe in a porcine survival study. Dis Esophagus. 2016 Aug 1;29(6):649–55.
15 Overwater A, Weusten B, Ruurda JP, van Hillegersberg R, Bennink RJ, de Keizer B, et al. Feasibility of sentinel node navigated surgery in high-risk T1b esophageal adenocarcinoma patients using a hybrid tracer of technetium-99 m and indocyanine green. Surg Endosc. 2021 Apr;36(4):2671–9.
16 Künzli HT, van Berge Henegouwen MI, Gisbertz SS, van Esser S, Meijer SL, Bennink RJ, et al. Pilot-Study on the feasibility of sentinel node navigation surgery in combination with thoracolaparoscopic lymphadenectomy without esophagectomy in early esophageal adenocarcinoma patients. Dis Esophagus. 2017 Nov 1;30(11):1–8.
17 Carey RW, Hilgenberg AD, Wilkins EW, Choi NC, Mathisen DJ, Grillo H. Preoperative chemotherapy followed by surgery with possible postoperative radiotherapy in squamous cell carcinoma of the esophagus: evaluation of the chemotherapy component. J Clin Oncol. 1986;4(5):697–701.
18 Forastiere AA, Gennis M, Orringer MB, Agha FP. Cisplatin, vinblastine, and mitoguazone chemotherapy for epidermoid and adenocarcinoma of the esophagus. J Clin Oncol. 1987;5(8):1143–9.
19 Hilgenberg AD, Carey RW, Wilkins EW, Choi NC, Mathisen DJ, Grillo HC. Preoperative chemotherapy, surgical resection, and selective postoperative therapy for squamous cell carcinoma of the esophagus. Ann Thorac Surg. 1988;45(4):357–63.
20 Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062–7.
21 Kelsen DP, Winter KA, Gunderson LL, Mortimer J, Estes NC, Haller DG, et al. Long-term results of RTOG trial 8911 (USA intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol. 2007;25(24):3719–25.
22 Ajani JA, Roth JA, Ryan B, McMurtrey M, Rich TA, Jackson DE, et al. Evaluation of pre- and postoperative chemotherapy for resectable adenocarcinoma of the esophagus or gastroesophageal junction. J Clin Oncol. 1990;8(7):1231–8.
23 Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med. 1998 Dec 31;339(27):1979–84.
24 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006 Jul 6;355(1):11–20.
25 Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. Lancet. 2019;393(10184):1948–57.
26 Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v38–49.
27 Shah MA, Kennedy EB, Catenacci DV, Deighton DC, Goodman KA, Malhotra NK, et al. Treatment of locally advanced esophageal carcinoma: ASCO guideline. J Clin Oncol. 2020;38(23):2677–94.
28 Gastric cancer treatment recommendations [Internet]. [cited 2021 Nov 24]. Available from: https://www.esmo.org/guidelines/gastrointestinal-cancers/gastric-cancer/eupdate-gastric-cancer-treatment-recommendations2.
29 Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996 Aug 15;335(7):462–7.
30 Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol. 2001 Jan 15;19(2):305–13.

31 Van Meerten E, Muller K, Tilanus HW, Siersema PD, Eijkenboom WMH, Van Dekken H, et al. Neoadjuvant concurrent chemoradiation with weekly paclitaxel and carboplatin for patients with oesophageal cancer: a phase II study. Br J Cancer. 2006 May 22;94(10):1389–94.
32 Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015 Sep 1;16(9):1090–8.
33 Oppedijk V, Van Der Gaast A, Van Lanschot JJB, Van Hagen P, Van Os R, Van Rij CM, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol. 2014 Feb 10;32(5):385–91.
34 Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D; ESMO Guidelines Committee. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016 Sep; 27(Suppl 5):v50–7.
35 Anderegg MCJ, van der Sluis PC, Ruurda JP, Gisbertz SS, Hulshof MCCM, van Vulpen M, et al. Preoperative chemoradiotherapy versus perioperative chemotherapy for patients with resectable esophageal or gastroesophageal junction adenocarcinoma. Ann Surg Oncol. 2017;24(8):2282–90.
36 Markar SR, Noordman BJ, Mackenzie H, Findlay JM, Boshier PR, Ni M, et al. Multimodality treatment for esophageal adenocarcinoma: Multi-Center Propensity-Score Matched Study. Ann Oncol. 2017;28(3):519–27.
37 Favi F, Bollschweiler E, Berlth F, Plum P, Hecheler D, Alakus H, et al. Neoadjuvant chemotherapy or chemoradiation for patients with advanced adenocarcinoma of the oesophagus? A Propensity Score-Matched Study. Eur J Surg Oncol. 2017;43(8):1572–80.
38 Stahl M, Walz MK, Riera-Knorrenschild J, Stuschke M, Sandermann A, Bitzer M, et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): long-term results of a controlled randomised trial. Eur J Cancer. 2017;81:183–90.
39 Von Döbeln GA, Klevebro F, Jacobsen AB, Johannessen HO, Nielsen NH, Johnsen G, et al. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastroesophageal junction: long-term results of a randomized clinical trial. Dis Esophagus. 2019;32(2):1–11.
40 Leong T, Smithers BM, Haustermans K, Michael M, Gebski V, Miller D, et al. TOPGEAR: a randomized, phase III trial of perioperative ECF chemotherapy with or without preoperative chemoradiation for resectable gastric cancer: interim results from an international, intergroup trial of the AGITG, TROG, EORTC and CCTG. Ann Surg Oncol. 2017; 24(8):2252–8.
41 Reynolds JV, Preston SR, O'Neill B, Lowery MA, Baeksgaard L, Crosby T, et al. Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol). (NCT01726452). J Clin Oncol. 2021 May 28;39(15 suppl):4004.
42 Hoeppner J, Lordick F, Brunner T, Glatz T, Bronsert P, Röthling N, et al. ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer. 2016;16(1): 1–10.
43 Reid BJ, Weinstein WM, Lewin KJ, Haggitt RC, VanDeventer G, DenBesten L, et al. Endoscopic biopsy can detect high-grade dysplasia or early adenocarcinoma in Barrett's esophagus without grossly recognizable neoplastic lesions. Gastroenterology. 1988;94(1): 81–90.
44 DeMeester TR, Attwood SE, Smyrk TC, Therkildsen DH, Hinder RA. Surgical therapy in Barrett's esophagus. Ann Surg. 1990; 212(4):528–2.
45 Pera M, Trastek VF, Carpenter HA, Allen MS, Deschamps C, Pairolero PC. Barrett's esophagus with high-grade dysplasia: an indication for esophagectomy? Ann Thorac Surg. 1992; 54(2):199–204.
46 Lerut T, Coosemans W, Van Raemdonck D, Dillemans B, De Leyn P, Marnette JM, et al. Surgical treatment of Barrett's carcinoma: correlations between morphologic findings and prognosis. J Thorac Cardiovasc Surg. 1994;107(4):1059–66.
47 Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111(1):30–50.
48 Hölscher AH, Bollschweiler E, Bumm R, Bartels H, Höfler H, Siewert JR. Prognostic factors of resected adenocarcinoma of the esophagus. Surgery. 1995;118(5):845–55.
49 Clark GWB, Peters JH, Ireland AP, Ehsan A, Hagen JA, Kiyabu MT, et al. Nodal metastasis and sites of recurrence after en bloc esophagectomy for adenocarcinoma. Ann Thorac Surg. 1994;58(3):646–54.
50 Siewert JR, Stein HJ. Barrett's cancer: indications, extent, and results of surgical resection. Semin Surg Oncol. 1997;13(4):245–52.
51 Hulscher JB, Van Sandick JW, Offerhaus GJ, Tilanus HW, Obertop H, Van Lanschot JJ. Prospective analysis of the diagnostic yield of extended en bloc resection for adenocarcinoma of the oesophagus or gastric cardia. Br J Surg. 2001;88(5):715–9.
52 Moon MR, Schulte WJ, Haasler GB, Condon RE. Transhiatal and transthoracic esophagectomy for adenocarcinoma of the esophagus. Arch Surg. 1992;127(8):951–5.
53 Stark SP, Romberg MS, Pierce GE, Hermreck AS, Jewell WR, Moran JF, et al. Transhiatal versus transthoracic esophagectomy for adenocarcinoma of the distal esophagus and cardia. Am J Surg. 1996 Nov;172(5):478–82.
54 Hulscher JBF, van Sandick JW, de Boer AGEM, Wijnhoven BPL, Tijssen JGP, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002 Nov 21;347(21):1662–9.
55 Omloo JMT, Lagarde SM, Hulscher JBF, Reitsma JB, Fockens P, Van Dekken H, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007 Dec;246(6):992–1000.
56 Ovrebo KK, Lie SA, Laerum OD, Svanes K, Viste A. Long-term survival from adenocarcinoma of the esophagus after transthoracic and transhiatal esophagectomy. World J Surg Oncol. 2012 Jun 30;10:130.
57 Van De Ven C, De Leyn P, Coosemans W, Van Raemdonck D, Lerut T. Three-field lymphadenectomy and pattern of lymph node spread in T3 adenocarcinoma of the distal esophagus and the gastro-esophageal junction. Eur J Cardiothorac Surg. 1999 Jun 1; 15(6):769–73.
58 Hagens ERC, Künzli HT, van Rijswijk AS, Meijer SL, Mijnals RCD, Weusten BLAM, et al. Distribution of lymph node metastases in esophageal adenocarcinoma after neoadjuvant chemoradiation therapy: a prospective study. Surg Endosc. 2020 Oct 1;34(10):4347–57.
59 Hagens ERC, van Berge Henegouwen MI, Gisbertz SS. Distribution of lymph node metastases in esophageal carcinoma patients undergoing upfront surgery: a systematic review. Cancers. 2020 Jun 1;12(6):1–18.
60 van Rijswijk AS, Hagens ERC, van der Peet DL, van Berge Henegouwen MI, Gisbertz SS. Differences in esophageal cancer surgery in terms of surgical approach and extent of lymphadenectomy: findings of an international survey. Ann Surg Oncol. 2019;26(7): 2063.
61 Hagens ERC, Van Berge Henegouwen MI, Van Sandick JW, Cuesta MA, Van Der Peet DL, Heisterkamp J, et al. Distribution of lymph node metastases in esophageal carcinoma [TIGER Study]: study Ppotocol of a Multinational Observational Study. BMC Cancer. 2019 Jul 4;19(1):662.
62 Biere SS, Maas KW, Bonavina L, Garcia JR, Van Berge Henegouwen MI, Rosman C, et al. Traditional invasive vs. minimally invasive esophagectomy: a multi-center, randomized trial (TIME-trial). BMC Surg. 2011 Jan 12;11:2.
63 Briez N, Piessen G, Bonnetain F, Brigand C, Carrere N, Collet D, et al. Open versus laparoscopically-assisted oesophagectomy for cancer: a multicentre randomised controlled phase III trial – the MIRO trial. BMC Cancer. 2011 Jul 23:11:310.
64 van der Sluis PC, Ruurda JP, van der Horst S, Verhage RJJ, Besselink MGH, Prins MJD, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer, a randomized controlled trial (ROBOT trial). Trials. 2012 Nov 30;13:230.

65 Biere SSAY, Van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, Garcia JR, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet. 2012;379(9829):1887–92.
66 Maas KW, Cuesta MA, Van Berge Henegouwen MI, Roig J, Bonavina L, Rosman C, et al. Quality of life and late complications after minimally invasive compared to open esophagectomy: results of a randomized trial. World J Surg. 2015 Aug 22;39(8):1986–93.
67 Voeten DM, Gisbertz SS, Ruurda JP, Wilschut JA, Ferri LE, van Hillegersberg R, et al. Overall volume trends in esophageal cancer surgery results from the dutch upper gastrointestinal cancer audit. Ann Surg. 2021 Sep 1;274(3):449–58.
68 Boone J, Livestro DP, Elias SG, Borel Rinkes IH, van Hillegersberg R. International survey on esophageal cancer: part I surgical techniques. Dis Esophagus. 2009;22(3):195–202.
69 Haverkamp L, Seesing MF, Ruurda JP, Boone J, V Hillegersberg R. Worldwide trends in surgical techniques in the treatment of esophageal and gastroesophageal junction cancer. Dis Esophagus. 2017 Jan 1;30(1):1–7.
70 Kuppusamy MK, Low DE. Evaluation of international contemporary operative outcomes and management trends associated with esophagectomy: a 4-year Study of >6000 Patients Using ECCG Definitions and the Online Esodata Database. Ann Surg. 2022;275(3):515–25.
71 Straatman J, Van Der Wielen N, Cuesta MA, Daams F, Roig Garcia J, Bonavina L, et al. Minimally invasive versus open esophageal resection: three-year follow-up of the previously reported randomized controlled trial: the TIME trial. Ann Surg. 2017 Aug 1;266(2):232–6.
72 Nuytens F, Dabakuyo-Yonli TS, Meunier B, Gagnière J, Collet D, D'Journo XB, et al. Five-year survival outcomes of hybrid minimally invasive esophagectomy in esophageal cancer: results of the MIRO randomized clinical trial. JAMA Surg. 2021 Apr 1;156(4):323–32.
73 de Groot EM, van der Horst S, Kingma BF, Goense L, van der Sluis PC, Ruurda JP, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open esophagectomy: long-term follow-up of a randomized clinical trial. Dis Esophagus. 2020 Nov 26;33(Suppl 2):doaa079.
74 Markar SR, Ni M, Gisbertz SS, van der Werf L, Straatman J, van der Peet D, et al. Implementation of minimally invasive esophagectomy from a randomized controlled trial setting to national practice. J Clin Oncol. 2020 May 18;38(19):2130–9.
75 Van Workum F, Verstegen MHP, Klarenbeek BR, Bouwense SAW, Van Berge Henegouwen MI, Daams F, et al. Intrathoracic vs. cervical anastomosis after totally or hybrid minimally invasive esophagectomy for esophageal cancer: a randomized clinical trial. JAMA Surg. 2021 Jul 1;156(7):601–10.
76 Jin D, Yao L, Yu J, Liu R, Guo T, Yang K, et al. Robotic-assisted minimally invasive esophagectomy versus the conventional minimally invasive one: a meta-analysis and systematic review. Int J Med Robot. 2019 Jun 1;15(3):e1988.
77 Angeramo CA, Bras Harriott C, Casas MA, Schlottmann F. Minimally invasive Ivor Lewis esophagectomy: robot-assisted versus laparoscopic-thoracoscopic technique. Systematic review and meta-analysis. Surgery. 2021;170(6):1692.
78 Tagkalos E, van der Sluis PC, Berlth F, Poplawski A, Hadzijusufovic E, Lang H, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus minimally invasive esophagectomy for resectable esophageal adenocarcinoma, a randomized controlled trial (ROBOT-2 trial). BMC Cancer. 2021 Sep 26;21(1):1060.
79 Hernandez JM, Dimou F, Weber J, Almhanna K, Hoffe S, Shridhar R, et al. Defining the learning curve for robotic-assisted esophagogastrectomy. J Gastrointest Surg. 2013 Aug;17(8):1346–51.
80 Sarkaria IS, Rizk NP, Grosser R, Goldman D, Finley DJ, Ghanie A, et al. Attaining proficiency in robotic-assisted minimally invasive esophagectomy while maximizing safety during procedure development. Innovations. 2016;11(4):268–73.
81 van der Sluis PC, Ruurda JP, van der Horst S, Goense L, van Hillegersberg R. Learning curve for robot-assisted minimally invasive thoracoscopic esophagectomy: results from 312 cases. Ann Thorac Surg. 2018 Jul 1;106(1):264–71.
82 Feike Kingma B, Hadzijusufovic E, van der Sluis PC, Bano E, Lang H, Ruurda JP, et al. A structured training pathway to implement robot-assisted minimally invasive esophagectomy: the learning curve results from a high-volume center. Dis Esophagus. 2020 Nov 1;33(Suppl 2):doaa047.
83 Claassen L, van Workum F, Rosman C. Learning curve and postoperative outcomes of minimally invasive esophagectomy. J Thorac Dis. 2019;11(1):S777–85.
84 Li B, Yang Y, Toker A, Yu B, Kang CH, Abbas G, et al. International consensus statement on robot-assisted minimally invasive esophagectomy (RAMIE). J Thorac Dis. 2020 Dec 1;12(12):7387.
85 Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. Ann Surg. 2007 May;245(5):777–83.
86 Metzger R, Bollschweiler E, Vallböhmer D, Maish M, DeMeester TR, Hölscher AH. High volume centers for esophagectomy: what is the number needed to achieve low postoperative mortality? Dis Esophagus. 2004;17(4):310–4.
87 Wouters MW, Gooiker GA, Van Sandick JW, Tollenaar RA. The volume-outcome relation in the surgical treatment of esophageal cancer: a systematic review and meta-analysis. Cancer. 2012 Apr 1;118(7):1754–63.
88 van der Sluis PC, van der Horst S, May AM, Schippers C, Brosens LAA, Joore HCA, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial. Ann Surg. 2019 Apr 1;269(4):621–30.
89 Sarkaria IS, Rizk NP, Goldman DA, Sima C, Tan KS, Bains MS, et al. Early quality of life outcomes after robotic-assisted minimally invasive and open esophagectomy. Ann Thorac Surg. 2019 Sep 1;108(3):920–8.
90 Kauppila JH, Xie S, Johar A, Markar SR, Lagergren P. Meta-analysis of health-related quality of life after minimally invasive versus open oesophagectomy for oesophageal cancer. Br J Surg. 2017 Aug 1;104(9):1131–40.
91 Young A, Gallesio JMA, Sewell DB, Carr R, Molena D. Outcomes of robotic esophagectomy. J Thorac Dis. 2021 Oct 1;13(10):6163.
92 Vimolratana M, Sarkaria IS, Goldman DA, Rizk NP, Tan KS, Bains MS, et al. Two-year quality of life outcomes after robotic-assisted minimally invasive and open esophagectomy. Ann Thorac Surg. 2021 Sep 1;112(3):880–9.
93 Williams AM, Kathawate RG, Zhao L, Grenda TR, Bergquist CS, Brescia AA, et al. Similar quality of life after conventional and robotic transhiatal esophagectomy. Ann Thorac Surg. 2022 Feb 1;113(2):399–405.
94 Mehdorn AS, Möller T, Franke F, Richter F, Kersebaum JN, Becker T, et al. Long-term, health-related quality of life after open and robot-assisted ivor-lewis procedures-A Propensity Score-Matched Study. J Clin Med. 2020 Nov 1;9(11):1–20.
95 Markar SR, Sounderajah V, Johar A, Zaninotto G, Castoro C, Lagergren P, et al. Patient-reported outcomes after oesophagectomy in the multicentre LASER study. Br J Surg. 2021 Sep 27;108(9):1090–6.
96 Jezerskyte E, van Berge Henegouwen MI, van Laarhoven HWM, van Kleef JJ, Eshuis WJ, Heisterkamp J, et al. Postoperative complications and long-term quality of life after multimodality treatment for esophageal cancer: an analysis of the Prospective Observational Cohort Study of Esophageal-Gastric Cancer Patients (POCOP). Ann Surg Oncol. 2021 Nov 1;28(12):7259–76.
97 Hamilton SR, Yardley JH. Regnerative of cardiac type mucosa and acquisition of Barrett mucosa after esophagogastrostomy. Gastroenterology. 1977 Apr;72(4 Pt 1):669–75.
98 Lord RV, Wickramasinghe K, Johansson JJ, DeMeester SR, Brabender J, DeMeester TR. Cardiac mucosa in the remnant esophagus after esophagectomy is an acquired epithelium with Barrett's-like features. Surgery. 2004;136(3):633–40.
99 Dunn LJ, Shenfine J, Griffin SM. Columnar metaplasia in the esophageal remnant after esophagectomy: a systematic review. Dis Esophagus. 2015 Jan 1;28(1):32–41.
100 da Rocha JR, Ribeiro U, Sallum RA, Szachnowicz S, Cecconello I. Barrett's esophagus (BE) and carcinoma in the esophageal stump (ES) after esophagectomy with gastric pull-up in achalasia patients: a study based on 10 years follow-up. Ann Surg Oncol. 2008 Oct;15(10):2903–9.

101 O'Riordan JM, Tucker ON, Byrne PJ, McDonald GSA, Ravi N, Keeling PWN, et al. Factors influencing the development of Barrett's epithelium in the esophageal remnant postesophagectomy. Am J Gastroenterol. 2004 Feb;99(2):205–11.
102 Fuchs HF, Schmidt HM, Meissner M, Brinkmann S, Maus M, Bludau M, et al. Endoscopic and histopathologic reflux-associated mucosal damage in the remnant esophagus following transthoracic esophagectomy for cancer-5-year long-term follow-up. Dis Esophagus. 2018 Jan 1;31(1):1–6.
103 D'Journo XB, Martin J, Rakovich G, Brigand C, Gaboury L, Ferraro P, et al. Mucosal damage in the esophageal remnant after esophagectomy and gastric transposition. Ann Surg. 2009 Feb;249(2):262–8.
104 Palmes D, Weilinghoff M, Colombo-Benkmann M, Senninger N, Bruewer M. Effect of pyloric drainage procedures on gastric passage and bile reflux after esophagectomy with gastric conduit reconstruction. Langenbecks Arch Surg. 2007 Mar 10;392(2):135–41.
105 Corsini EM, Mitchell KG, Zhou N, Antonoff MB, Mehran RJ, Rajaram R, et al. Intestinal metaplasia in the esophageal remnant is rare after ivor lewis esophagectomy. J Gastrointest Surg. 2021 Sep 1;25(9):2185–91.