Contents

Esophageal Cancer

Introduction

This is an abbreviated guide to treatment protocols at the Levine Cancer Institute. They are designed to provide referring physicians and our trainees with general guidelines. In most cases, these cases are best cared for in a multidisciplinary environment. Caring for patients with GI cancers is clearly a 'team support' making use of the wisdom and experience of a broad-based teams of practitioners. These guidelines are not presented as 'Standard of Care.' Readers interested in 'Standard of Care' treatment protocols are referred to the National Comprehensive Cancer Network (NCCCN) Guidlines, which can be found at NCCN.org.

Chapter 1

Overview

Esophageal cancers can be grouped into 4 treatment categories:

- Superficial → Endoscopic therapy
- Localized → Primary surgery
- Locally Advanced → Trimodality therapy
- Metastatic → Systemic therapy

Patients with minimal dysphagia, no weight loss, and small (<3cm length) tumors are evaluated with endoscopic ultrasound:

- If uT1 on EUS and <2cm in size, endoscopic mucosal resection yields more information and may be therapeutic for tumors with negative margins and without high-risk features.
- If uT2N0 on EUS, and PET scan shows a small tumor (MTV <10cm^3), primary surgery is preferred in patients who are good surgical risks
- If T3 or N+ on EUS, if PET shows no metastatic disease, trimodality therapy is optimal)

Patients with dysphagia to solids or weight loss or tumor length >3cm are unlikely to have T1-2 tumors and can be evaluated with PET scan.

- If PET shows disease confined to the esophagus and regional nodes, trimodality therapy (chemoradiation followed by surgery) is optimal.
- If PET shows metastatic disease, patients are eligible for palliative chemotherapy with radiation for treatment of symptoms of dysphagia.
- If PET shows extra-regional lymph node disease, patient is at high risk for distant disease and can be treated with induction chemotherapy followed by chemoradiation and surgical evaluation.

Chapter 2

Staging

The staging workup begins once a diagnosis is made on endoscopy.

The first step is to make a preliminary determination whether the tumor is early stage (and can be treated with endoscopy or primary surgery) or later stage (and treated with chemoradiation followed by surgery or with)

The diagnostic studies needed for these treatment groups are different, so the workup can be make more efficient by sorting patients at presentation in to two groups:

Patients with minimal dysphagia, no weight loss, and tumors with less than 3cm cranio-caudal extent have a reasonable change of being T1 or T2 tumors. Tumors <3cm in length are much more likely to represent T1-2 lesions than those $\geq$ 3cm(Hollis et al., 2017)

Superficial and Localized tumors generally present with minimal dysphagia or weight loss. These tumors may present with bleeding, or dysphagia without weight loss. For these patients, determining the precise T stage is important in their workup, so **endoscopic ultrasound** is the most frequent staging study after diagnosis.

Locally-advanced or metastatic tumors tend to present with dysphagia and weight loss. At first approximation, these tumors are usually clinical T3 lesions, and the important bifurcation in their treatment is the presence or absence of metastatic disease. For patients with dysphagia and weight loss, **PET** is the most frequent initial staging study after diagnosis.

Patients who present with dysphagia are likely to have T3 or T4 disease, which is generally treated with neoadjuvant chemoradiation followed by surgery. Data from Memorial Sloan Kettering [Ripley 226] among 61 patients with esophageal cancer who presented with dysphagia, 54 (89%) were found on EUS to have uT3-4 tumors. On the other hand, among 53 patients without dysphagia, 25

(47%) were uT1-2, and were potentially candidates for primary surgery. Their conclusion was that EUS could be omitted from the workup of patients with dysphagia, but is useful in patients without dysphagia.

PET can be helpful in evaluating patients who may have T1-2 disease, and might be candidates for primary surgical therapy. A comparison of PET and EUS [malik,claxton,1] showed that uT1-2 tumors had median metabolic tumor volume (MTV) of 6.7cm^3, compared with uT3-4 tumors, with a median SUV of 35.7cm^3.

Chapter 3

Superficial Esophageal Cancer

Superficial esophageal cancer is usually asymptomatic, which means that the diagnosis is generally made in the context of surveillance for Barrett's esophagus.

Nodular Barrett's esophagus can be best evaluation with endoscopic mucosal resection, which can provide further staging information if an adenocarcinoma is found, such as depth of invasion, differentiation, and lymphovascular invasion.

Larger lesions should first be evaluated with endoscopic ultrasound (EUS)?

EUS is less sensitive for T1 lesions (Bergeron et al., 2014) -> use EMR for diagnosis (Maish and DeMeester, 2004)

(Should nodular Barrett's be evaluated with EUS prior to EMR?)

T1a tumors have a low risk of nodal metastasis (Dunbar and Spechler, 2012)

3.1 Endscopic Mucosal Resection (EMR)

For patients with nodular Barrett's esophagus or small tumors judged to be T1 by endoscopic ultrasound, endoscopic mucosal resection (EMR) can be diagnostic and potentially curative.(Thomas et al., 2009)

EMR also helps establish the difference between T1a and T1b compared with pathology (Worrell et al., 2018)

EMR is likely sufficient for small tumors with favorable patholgic factors(Pech et al., 2014) (Nurkin et al., 2014):

- Size less than 2cm
- Lateral and deep margins clear

- Absence of lymphovascular invasion
- Well- or moderately- differentiated

EMR: (Soetikno et al., 2005)

See MOlina JTCVS 153:1206

EMR for high-grade dysplasia (Shaheen et al., 2009)

EMR for low-grade dysplasia (Phoa et al., 2014) resulted in 25% riskd reduction in progression go HGD.

Endoscopic submucosal dissection is a technique for deeper endoscopic removal of esophageal lesions using endoscopic cautery, which dissects through the submucosa. ESD has a higher rate of curative resection (Cao et al., 2009) albiet at the cost of prolonged operative times and increased risk of complications such a bleeding. (Repici et al., 2010)

ESD takes more time and has higher R0 resection rate but similar recurrence erate at 2 eyars (Terheggen et al., 2017)

Need for RFA of Barrett's after EMR: (Haidry et al., 2013) Combination therapy with EMR and RFA results in lower rate of recurence than EMR alone.(Pech et al., 2008)

RFA for Barrett's national registry (Ganz et al., 2008)

Chapter 4

Localized Tumors

4.1 T1b Tumors

4.2 T2N0 Tumors

Multiple studies have failed to show the additional benefit of chemotherapy or chemoradiation for pT2N0M0 esophageal cancer patients treated with radiation.

Neoadjuvant chemo not likey to be helpful for early stage disease - FFCD 9901 [Mariette 2416] enrolled patients with T1-2 or T3N0 tumors to chemoradiation followed by surgery versus surgery alone. The majority of the tumors (72%) were squamous cell carcinoma.Postoperative mortality was significaly increased in the chemoradiation arm (11.1% vs 3.4%).

Meta-analysis of 5265 patients in 10 studies showed that while neoadjuvant therapy was associated with a reduction in positive margin rate, there was no difference in terms of recurrence or survival.[MOta 176]

French trial FREGAT(Markar et al., 2016)

Retrospective review of the National Cancer DataBase failed to demonstrate a difference in survival of cT2N0M0 esophageal cancer with or without preoperative chemoradiation.(Speicher et al., 2014)

A retrospective report from Johns Hopkins examined outcomes of T2N0 squamous cell carcinoma patients and showed equivalent outcomes for primary surgery vs neoadjuvant chemoradiation followed by surgery (Zhang et al., 2012)

4.3 Staging of T2N0 Tumors

The challenge for treatment decision-making is the limited sensitivity of endoscopic ultrasound in ruling out pT3 or pN+ disease. In other words, if a patient

who is thought to have cT2N0 disease undergoes resection, and is found on pathology to have pT3 or pN^+ disease, this would dictate the need for post-operative chemoradiation. In general, chemoradiation after esophagectomy is difficult for patients to tolerate, with a _____ % chance of failure to complete therapy.

Data from the Cleveland Clinic looked at 53 patients judged to be T2N0 by endoscopic ultrasound (uT2N0) were treated with primary surgery. Pathologic examination showed that 17 (37%) were understaged by endoscopic ultrasound, and were pathologic (pT3) in 4 or node positive (pN^+) in 13 cases. These patients were treated with postoperative adjuvant chemoradiation.(Rice et al., 2007)

It is critical, therefore, in patients for whom primary surgery is contemplated, to attempt to identify those with occult T3 or N+ disease.

Patients who appear to have limited stage disease benefit from evaluation with a combination of

See also PMID:25047477

(MTV)

(Tumor Length)

(dysphagia)

##Primary Surgery {#primary_surgery}

NCCN recommends PET scanS

Most common sites of metastasis are liver, lung, bones, adrenal.

PET detects occult metastasis in 10-20% of cases (Kato et al., 2002, Kim et al. (Apr)). Among 129 patients with esophageal cancer, PET detected additional sites of disease in 41% and changed management in 38% (Chatterton et al., 2009)

PET for restaging detects interval development of metastatic disease in 8-17% of cases (van Vliet et al., 2008)

Chapter 5

Locally Advanced Cancer

Tumors that are T2N$^+$M0 or T3NxM0 are considered locally-advanced. The high rate of failure with surgery alone has led to development of adjunctive therapies.

5.1 Trimodality Therapy

Trimodality therapy consists of chemoradiation followed by surgery.

CROSS trial randomized 364 patients with resectable esophageal and gastroesophageal junction tumors (75% adenocarcinoma) to neoadjuvant chemoradiation consisting of 4,140 cGy of radiation with concurrent carboplatin and paclitaxel or surgery alone.(van Hagen et al., 2012) Clinical node-positive disease was present in 16%. Pathologic complete response was seen in 23% of adenocarcinoma and 49% of squamous cell carcinomas. Median overall survival was 49 months after trimodality vs 24 months after surgery alone (p=0.003). Squamous cell carcinomas appeared to have particular benefit, with a hazard ratio of 0.42 for squamous cell vs 0.74 for adenocarcinoma. Median survival was improved for adenocarcinoma from 27.1 months to 43.2 months, but the median survival for squamous cell increased from 27.1months to 81.6 months for squamous cell. Rate of R0 resection was higher with chemoradiation (92% vs 69% p<0.001) andlocal recurrence rates lower (14% vs 34% P<0.001), and peritoneal recurrence lower (4% vs 14% P<0.001). Despite the relatively low dose of radiation, in-field recurrences were less than 5%. The primary cause of failure was distant disease (31%) and local/regional failure (14%).(Oppedijk et al., 2014)

Alternative to carbotaxol is FOLFOX (SOG trial (Leichman et al., 2011))

Ogoing PROTECT trial ompares FOLFOX to paclitaxel and carbo (Messager et al., 2016)

5.1.1 Neoadjuvant chemoRT for SCCA

NeoCRTEC5010 (Yang et al., 2018)

Meta-abalysis of chemoRT vs chemo (Zhao et al., 2018)

5.2 ChemoRT vs Trimodality therapy

The sensitivity of squamous cell carcinoma of the esophagus to chemoradiation has raised the question whether

Stahl Locally advanced squamous cell carcinoma randomized to induction chemotherapy (cisplatin, etopiside, 5FU with leuocovrin) followed by chemoradiation (4000cGy with concurrent ciplatin and etopiside) followed by surgery compared with induction chemotherapy followed by chemoradiation (6400cGy with concurrent cisplatin and etopiside).(Stahl et al., 2005) progression-free survival was better in the trimodality group (64.3% vs 40.7%) Treatment-related morality was substantial in the surgery arm (13% vs 4%). This would be considered an excessive rate of operative mortality by modern standards. Unsurprisingly, there was no difference in overall survival between groups, in part because the surgical group had an excess 9% mortality rate from treatment. Two-year survival in the surgery arm was 40% vs 35% in the definitive chemoradiation arm. (**?**)

In the French FFCD trial, 444 patients with carcinoma of the esophagus (90% squamous cell) were treated with two cycles of 5-FU and cisplatin with concurrent radiation.(Bedenne et al., 2007) Patients with a partial or complete clinical response to chemoradiation were randomized to either surgery or a boost of radiation. Patients who did not respond to chemoradiation were treated with surgery and were eliminated from the study. Only 259 of the original 444 patients (59%) went on to randomization, with the remainder (those not responding to chemoradiation) treated with surgery. Of the randomized group, median survival was 17.7months in the surgery arm versus 19.3months in the definitive chemoradiation arm. Like the Stahl study, treatment-related mortality in the surgical arm was high (9% versus 1%).

5.2.1 Neoadjuvant chemotheraphy followed by surgery

POET Trial (Pre-Operative therapy in Esophageal adenocarcinoma Trial) treated patients with adenocarcinoma of the gastroesophageal junction with either neoadjuvant chemotherapy (5-FU, leucovorin, cisplatin) followed by surgery or induction chemotherapy with the same agents, followed by chemoradiation (4000cGy with concurrent cisplatin and etoposide). The study failed to meet its accrual goal, but there was a suggestion of improved 3-year survival with preoperative chemoradiation (47.4% vs 27.7% p=0.07) as well as improved local control (76.5% vs 59%). In addition, chemoradiation was associated with a higher pathologic complete response rate (15.6% vs 2%)(Stahl et al.,

2009). A meta-analysis of 33 randomized trials further suggested a greater benefit from neoadjuvant chemoradiation followed by surgery compared with neoadjuvant chemotherapy followed by surgery(Pasquali et al., 2017) and a similar meta-analysis (Sjoquist et al., 2011)

#Active Surveillance

EGD is poor predictor of pCR (Sarkaria et al., 2009)

5.3 GE Junction

(Siewert et al., 2006)

5.4 Induction chemotherapy followed by chemoRT

See NCCN pages M-25 and M-26

Stahl (Stahl et al., 2009) randomized patients to preoperative chemotherapy (A) vs preoperative chemotherapy followed by preoperative chemoradiation (B). Higher pcR rate in arm B (15.6% vs 2%) and ypN0 resection (64.4% vs 37.7%).

5.5 Postoperative chemoradiation

Intergroup-0116 (Macdonald et al., 2001) (Smalley et al., 2012) treated 556 patients with adenocarcinoma of the stomach or GE junction with surgery along vs surgery followed by postoperative chemoradiation. After a median followup of over 5 years, median overall survival iin the surgery alone group was 27 months vs 36 months in the postoperative chemoradiation group (p=0.005) Decrease in local failure as the first site of failure in the chemoradiation group (19% versus 29%).

Chemoradiation afte resectdion of GE junction tumors (Kofoed et al., 2012) among a group of 211 patients with GE junction adenocarcinoma with positive lymph nodes with improved 3-year disease-free survival (37% s 24%).

Chapter 6

Definitive ChemoRT

6.1 Phase II Studies

Experience with patients who refuse surgery or are medically unfit:

(Taketa et al., 2012) (**?**) (**?**)

Castoro(Castoro et al., 2013)

preSANO(**?**) Clinical Response evaluation after chemoRT for esophageal cancer with PET and EGD.

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Stahl Locally advanced squamous cell carcinoma randomized to induction chemotherapy (cisplatin, etopiside, 5FU with leuocovrin) followed by chemoradiation (4000cGy with concurrent ciplatin and etopiside) followed by surgery compared with induction chemotherapy followed by chemoradiation (6400cGy with concurrent cisplatin and etopiside).(Stahl et al., 2005) progression-free survival was better in the trimodality group (64.3% vs 40.7%) Treatment-related morality was substantial in the surgery arm (13% vs 4%). This would be considered an excessive rate of operative mortality by modern standards. Unsurprisingly, there was no difference in overall survival between groups, in part because the surgical group had an excess 9% mortality rate from treatment. Two-year survival in the surgery arm was 40% vs 35% in the definitive chemoradiation arm. (**?**)

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#Active Surveillance

EGD is poor predictor of pCR (Sarkaria et al., 2009)

Chapter 7

Radiation for esophageal cancer

RTOG 94-05 clinical trial (Minsky et al., 2002)

7.1 Salvage esophagectomy

(Markar et al., 2014)

(Swisher et al., 2002)

Chapter 8

Surgery

Three general approaches exist for surgical therapy.

Trans-thoracic or Ivor Lewis esophagectomy(Visbal et al., 2001) removes the intrathoracic portion of the esophagus and constructs an anastomosis within the chest. The approach include an abdominal phase, during which an esophageal substitute is constructed (usually from stomach). A thoracic phase then removes the intrathoracic esophagus and constructs an anastomosis within the chest cavity.

A McKeown esophagectomy utilizes three surgical fields: abdomen, right chest, and neck. The right chest approach allows dissection of peri-esophageal lymph nodes, and the cervical incision allows removal of the total esophagus.(McKeown, 1976) This approach is useful for tumors which involve the proximal thoracic esophagus, to ensure a negative margin. The cervical anastomosis carries a higher risk of anastomotic leak than a thoracic anastomosis, although the morbidity of a cervical anastomosis leak is less serious than that of a leak of a thoracic anastomosis.

A transhiatal esohpagectomy approaches the esophagus from the abdomen through the hiatus and from neck. By blunt dissection the esophagus is freed up without the need for thoracotomy. An esophageal substute is then brought from the abdomen to the neck through the mediastinum(Orringer and Sloan, 1978) (Orringer et al., 2007)<! – Orringer Ann Surg 2007 –> The operation is designed to avoid the pulmonary toxicity of the right chest approach. On the other hand, the blunt nature of the mediastinal dissection means that fewer lymph nodes are harvested than with a trans-thoracic approach.

Randomized trial of transthoracic esophagectomy with extended lymph node dissection versus transhiatal esohpagectomy showed fewer pulmonary complications with the transhiatal approach. (Hulscher et al., 2002) Fewer lymph nodes were havested with a transhiatal appraoch. A post-hoc analysis showed that

among patients with 1-8 positive lymph nodes, survival with improved with the extended lymph node dissection.(Omloo et al., 2007)

Minimally-invasive approaches to esophagectomy are now common, with evidence for less perioperative morbidity than an open approach (Biere et al., 2012) (Zhou et al., 2015)

Randomized trial of a hybrid MIE (with laparoscopy and thoracotomy) was associated with lower postoperative complications than open esophagectomy (Mariette et al., 2019)

High volume (Birkmeyer et al., 2003) (Wouters et al., 2009)

Siwert III lesions are considered gastric cancers (Rusch, 2004) (Siewert et al., 2006)

Laparoscopy may be helpful in Siewert III tumors (de Graaf et al., 2007)

8.0.1 Preoperative Evaluation

Dysphagia can be scored accordgin to Mellow et al (Mellow and Pinkas, 1985):

- 0 No dysphagia
- 1 Dysphagia to normal solids
- 2 Dysphagia to soft solids (ground beef, poultry,fish)
- 3 Dysphagia to solids and liquids
- 4 Inability to swallow saliva

8.1 Minimally-invasive Esophagectomy

Higher lymph node yield with MIE vs open approach [Kalff]

8.2 Transthoracic

8.3 Transhiatal

8.4 Three-hole

8.5 Extended lymphadenectomy

Chapter 9

Metastatic

9.1 Palliative radiation

Palliative radiation vs chemoradiation (Penniment et al., 2018)

Radiation along favored over chemoradiation in the palliaitve setting (Penniment et al., 2018)

9.2 Chemoradiation vs chemotherapy in Stage IV

(Guttmann et al., 2017)

Chapter 10

Stents for malignant disease

(Vakil et al., 2001)

Review of guidelines 2010 Am Society GI (Sharma et al., 2010)

Chapter 11

Surveillance

11.1 T1a treated with endoscopic resection

EGD every 3 mo for first year, then every 6 months for second year, then annually(Shaheen et al., 2016)

11.2 Tib treated with endoscoic resection

EGD every 3 mon for first year, then every 4-6 months for seond year, then annually CT chest/abdomen every 12 months for up to 3 years (as clinically indicated)

11.3 T1b treated with esophagectomy

EGD every 3-6 months for first 2 years, then annually for 3 more years. CT every 6-9 months for first 2 years, then annually up to 5 years.

11.4 Stage II or III treated with chemoradiation.

These patients are at risk for local recurrence (Sudo et al., 2014) and some may be candidates for salvage esophagectomy. Most relapses (95%) occur within 24 months. See also (Taketa et al., 2014)

11.5 Locally-advanced treated with trimodality therapy

Local/regional relapses are uncommon. (Dorth et al., 2014) (Oppedijk et al., 2014) (Sudo et al., 2013) => NCCN does not recommend EGD. 90% of relapses occur within 36 months of surgery.

CT every 6 months up to 2 years (if patient is a candidate for additional curative-intent therapy)

Chapter 12

Survivorship

12.1 Nutritional consequences

(Baker et al., 2016)

Weight loss (Martin and Lagergren, 2009) (Ouattara et al., 2012)

12.2 Cardiac toxicity of radiation

(Beukema et al., 2015) (Frandsen et al., 2015) (Gharzai et al., 2016)

Gastric Cancer

Chapter 13

Overview

Chapter 14

Superficial

Chapter 15

Locally-Advanced Gastric

Locally-advanced gastric cancer (T3 or N^+) is generally treated with some form of adjuvant therapy, which has been shown to improve upon the outcomes with surgery alone.

15.1 Preoperative Chemotherapy

FLOT chemotherapy (Al-Batran et al., 2019)

MAGIC study randomized 503 patients to perioperative 'sandwich' therapy consisting of epirubicin, cisplatin, and 5-FU versus surgery alone. In the perioperative chemotherapy group, 4 cycles were administered prior to surgery, and 4 cycles afterwards. Tumors of the esophagus or gastroesophageal junction comprised 26% of the study population. While over 90% of patients assigned to the chemotherapy arm completed their preoperative chemotherapy, only 66% completed their postoperative therapy. Survival at 5 years was 36% in the perioperative chemotherapy group, compared with 24% in the surgery group ($p<0.001$).(Cunningham et al., 2006)

CLASSIC clinical trial randomized 1033 patients with stage II or III gastric cancer after D2 gastrectomy to 6 months of adjuvant chemotherapy versus surgery alone. Three-year survival was improved in the chemotherapy group (74% *v* 59%).(Bang et al., 2012)

The FFCD trial randomized patients to preoperative chemotherapy with 2 or 3 yccles of cisplatin and 5-FU versus surgery alone. Tumors of the lower esophagus or gastroesophageal junction comprised 75% of the study population. Survival at 5 years was longer in the chemotherapy group (38%) versus 24% in the surgery alone group ($p=0.02$).(Ychou et al., 2011)

15.2 Postoperative chemotherapy

CLAASIC trial (Noh et al., 2014) (Bang et al., 2012) patients with II or IIIB gastric cancer received gastrectomy with D2 node dissection randomized to postoperative chemotherapy with capecitabine and oxaliplatin. Chemotherapy group had improved 3-year DFS (74% vs 59% P<.0001)

Chapter 16

Locally Advanced Gastric Ca

16.1 Postoperative chemoradiation

Intergroup 0116 trial (Macdonald et al., 2001) Surgical quality control was poor, as 90% were treated a limited lymph node dissection. Long-term followup, however (Smalley et al., 2012) showed a persistent benefit of postoperative chemoradiation.

ARTIST trial 450 patients treated with a D1 α gastrectomy were randomized to adjuvant capcitibine and cisplatin versus chemoradiation consisting of two cycles of capcitabine/oxalipaltin followed by chemoradiation followed by chemotherapy. Overall 3- year survival did differ between groups (78.2% vs 74.2% p =0.86). A post-hoc analysis of patients with positive nodes showed a beneficial effect of chemoradiation (77.5% *v* 72.3% p=0.365).(Lee et al., 2012)

CRITICS trial treated all patients with preoperative chemoterhapy followed by surgery. Postoperative patients were then randomized between additional chemotherapy versus chemoradiation.

16.2 Preoperative chemoradiation

(Ajani et al., 2006)

Chapter 17

Neoadjuvant Chemotherapy for colon cancer

Seymour MT, Morton D. FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer. J Clin Oncol. 2019 May;37(15 Suppl):3504-3504.

Chapter 18

Extended Node dissection for colon cancer

Short-term outcomes of complete mesocolic excision versus D2 dissection in patients undergoing laparoscopic colectomy for right colon cancer (RELARC): a randomised, controlled, phase 3, superiority tria

Short-term outcomes of a multicentre randomized clinical trial comparing D2 versus D3 lymph node dissection for colonic cancer (COLD trial). Karachun A, Panaiotti L, Chernikovskiy I, Achkasov S, Gevorkyan Y, Savanovich N, Sharygin G, Markushin L, Sushkov O, Aleshin D, Shakhmatov D, Nazarov I, Muratov I, Maynovskaya O, Olkina A, Lankov T, Ovchinnikova T, Kharagezov D, Kaymakchi D, Milakin A, Petrov A. Br J Surg. 2020 Apr;107(5):499-508. doi: 10.1002/bjs.11387. Epub 2019 Dec 24. PMID: 31872869 Clinical Trial.

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