

The perspectives of barriers and enablers in implementing “non-tube no fasting”-enhanced recovery system after esophagectomy

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Abstract

The dreadful suffering of thoracic gastric conduit-related complications after an esophagectomy has always driven surgeons on the frontlines to seek novel and efficient strategies towards developing a sustainable program known as Enhanced Recovery After Surgery (ERAS). Among the conventional approaches to ERAS such as refining surgical operations, optimizing the rehabilitation procedures, and minimizing nutritional risks, the earlier resumption of food intake orally and minimization of tubes for drainage are increasingly recognized due to the apparent benefits they bring to patients. With an in-depth understanding of natural feeding strategies and the innovations and improvements of relevant techniques, "none tube no fasting (NTNF)" mode is starting to be accepted by mainstream medical workers worldwide. The author here timely summarizes and discusses the evolution of the feeding strategy after esophageal surgery with a specific focus on the origin and development of NTNF. Notwithstanding the various challenges of the current treatment regimen, the accumulation of first-hand experience, advancements of new technologies, and the combined strategies of multimodality treat-

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ments including ESD and EMR, will allow the NTNF-ERAS system to gradually be perfected. Through this will be ushered a new era of esophageal surgery, allowing it to reach new heights and ultimately benefit the wellbeing of esophageal cancer patients across the globe.

Keywords: Esophagectomy, Enhanced recovery after surgery, Esophageal cancer

Introduction

Surgical management of esophageal cancer often entails an esophagectomy, lymphadenectomy, and reconstruction of the upper gastrointestinal tract. The inevitable preoperative reduction of human wellbeing may be amplified or accelerated by subsequent surgical tissue injuries, pathophysiological responses, gastrointestinal anatomical changes, and malfunctions of esophagus. In retrospective of a hundred years of modern esophagectomy history, despite the tremendous advances that have been made in the minimally invasive approaches and anastomotic techniques, the overall complication rate is still fluctuating between 24% and 64%^[1,2]. Among various morbidities, thoracic gastric conduit-related complications dampen the surgeons' enthusiasm and interest in developing esophagectomy. The prevention of thoracic gastric conduit-related complications has always been challenging. Its relatively steep and difficult learning curve has likely been its Achilles heel, slowing adoption somewhat; however, its incorporation into the Enhanced Recovery After Surgery (ERAS) program is currently a strong driving force for renewed interest.

ERAS combines various perioperative patient care methods that integrate evidence-based interventions that can reduce surgical stress, maintain the postoperative physiological function, and accelerate recovery in patients undergoing esophagectomy. The ERAS program involves the application of the best bundled practices to improve the value of perioperative care, which includes emphasizing preoperative preparation, refining surgical procedures, and opti-

mizing rehabilitation programs. ERAS is always a compromise among surgical safety, perioperative wellbeing, nutritional risk, patient report outcomes (PROs), and financial costs^[3-6]. Major ERAS barriers in esophagectomy must be overcome for future progression through multidisciplinary collaboration, including shorter days before resuming oral intake and fewer tubes for drainage or nutrition postoperatively. The placement of a nasojejun tube or a feeding jejunostomy is a conventional procedure used during esophagectomy. However, it is still contrary to natural feeding philosophy and may yield discomfort and complications postoperatively^[4,6,7]. The benefits of removing such barriers are self-evident; however, the technical challenges posed by these tasks remain daunting.

Through innovations and improvements to current systems, we presented the “none tube no fasting (NTNF)” mode to upgrade ERAS^[6-8] and promote PROs^[9]. The NTNF coincides with conventional long-term fasting and tube-centered management and has been widely questioned since its first onset regarding its harm to the anastomotic integrity and gastric conduit. This review will focus on the history of feeding strategies after esophagectomy, the theoretical basis and critical technology of NTNF, and the current challenges and future directions.

The historical evolution of feeding strategies after esophagectomy

Since the chief complaint of locally advanced esophageal cancer is usually dysphagia, one of the tasks of surgical management for it is to resume the oral intake. The first successful modern surgical treatment case was reported in 1913, when Dr. Franz Torek performed a partial esophagectomy with gastroesophagostomy via left thoracotomy on a 67-year-old female esophageal cancer patient^[10]. The patient resumed oral intake of semi-liquid food on the eighth postoperative day via a rubber tube, and she survived for 13 years relapse-free^[11]. Subsequently, modern esophageal surgery experienced three stages: (1) an-

esthetic and intraoperative safety, (2) radicality of resection, and (3) focusing on the quality of life after surgery ^[12].

The advent of diverse approaches, including Ivor Lewis', McKeown's, Sweet's, and Orringer's esophagectomy, three-field lymph node dissection, and en-bloc resection strategies during the exploration phase, is a tribute to the surgical evolutionary pathways ^[13]. After a century of journey, the safety challenges of this high-risk surgery still haunt most surgeons. In the initial phase of esophagectomy, many scholars have conducted deep research on the safe perioperative management, including anesthesia, procedure, and intense care. The results are fruitful yet still insufficient. Physicians remain wary of resuming early oral intake after surgery when responding to risks of anastomotic leakage, aspiration, or malnutrition. Most are more inclined toward a preventive jejunum stoma, firstly reported by Gerndt and Orringer in 1994 ^[14] for enteral nutrition in the abdominal phase during surgery, which has been regarded as an essential measure in Western countries.

A multicenter randomized controlled trial by Lassen et al. ^[15] assessed the safety outcomes of early oral feeding after gastroesophageal surgery by comparing it with conventional tube feeding. It turned out that early oral intake did not lead to significantly greater postoperative morbidity but shortened the time of bowel function recovery and length of hospital stay. However, there were only two patients who underwent esophagectomy. In 2007, we conducted exploratory research on early oral feeding (starting on postoperative day 2, POD 2) after esophagectomy ^[16]. Eighty patients in total enrolled and revealed no postoperative anastomotic leak or aspiration pneumonia. It indicated the beginning of an era when the NTNF mode was embedded into the Chinese ERAS program.

Advancement in the early oral feeding strategy after esophagectomy

In recent years, the early oral feeding strategy after esophagectomy has remained beyond the hori-

zon, scaling from proof-of-concept to non-inferiority phase 3 trial. Most retrospective studies reported that early oral feeding was associated with unfavorable outcomes. Eberhard and colleagues reviewed 359 esophageal cancer cases and compared morbidities among different timing of resuming oral intake after surgery ^[17], and found that the early oral feeding group (three days after surgery) had significantly higher risks of anastomotic leakage (9% vs. 2%), stricture (27.7% vs. 15.8%), and pneumonia (39% vs. 31%) compared to the late feeding group (15 days after surgery). A retrospective study of 203 patients undergoing transhiatal esophagectomy without thoracotomy demonstrated significantly higher risks of anastomotic leakage (14.5% vs. 4.2%, $P = 0.0089$) and stricture (27.7% vs. 15.8%, $P = 0.05$) in the early oral intake group (within POD 3), compared to the delayed oral intake group (after POD 15) ^[18].

In 2007, 80 patients from our prospective, single-center, exploratory cohort study resumed oral intake of fluid food on POD 2. All patients were discharged within the first week after surgery, having no anastomotic leak ^[16]. In 2015, Mahmoodzadeh and colleagues conducted a prospective study ^[19]. They found that early oral feeding after thoracotomy for upper gastrointestinal cancer facilitates early bowel functional recovery, shortens the length of stay, and decreases the risk of re-admission. In 2018, we firstly reported that the postoperative morbidity risk of the early oral feeding (POD 1) group was non-inferior to the later oral feeding (POD 7) group after esophagectomy (30.0% vs. 32.9%) ^[20], and with a faster recovery rate of cytokines, including IL-6, IL-8, TNF α , and MCP-1, indicating facilitation of stress recovery ^[21]. Recently, an international multicenter, randomized controlled study (NUTRIENT II) revealed that there were no significant differences in functional recovery (7 days vs. 8 days, $P = 0.436$), anastomotic leakage (18.5% vs. 16.4%, $P = 0.757$), or pneumonia (24.6% vs. 34.3%, $P = 0.221$) after esophagectomy between early (POD 1) and late oral feeding (POD 5), but a higher incidence of chyle leakage in late oral feeding

group^[22].

The conception, innovation, and kernel composition of NTNF mode

The NTNF mode was conceived using our exploratory and randomized controlled studies. To implement NTNF mode, the first task is to reduce the risk of anastomotic leakages, then to deal with the restoration of gastric emptying.

To reduce anastomotic leak hazards, we compared different anastomotic techniques available and categorized them as single-layer and double-layer approaches. While each method has pros and cons, the choice mostly boils down to the surgeon's preference. However, the potential risk of the anastomotic leakage remains high^[23]. Our original triple-layer with embedment anastomotic technique, "Li's Anastomotic Technique," significantly decreases the rate of anastomotic leakage^[23-24]. Besides the anastomotic method, we believe that the gastric-protection maneuvers are the key components to reducing risks of anastomotic and thoracic conduit complications, which include preventing grasping or clamping of the gastric conduits, stapling line enhancement with continuous sutures, and thermal management during making gastric conduits. Our previous study indicated that through benefiting from "Li's Anastomotic Technique," patients could resume oral intake nutrition on POD2, and the incidence of anastomotic leakage dropped to 2%^[20].

Regarding the gastric emptying issue, we conducted serial evaluations on the entirety of stomach and gastric conduit emptying. We found accelerated gastric emptying after surgery due to intake of liquid food, which may relate to the anatomical change of the stomach^[25]. The transition of the gastric long-axis from horizontal to vertical makes the connecting line between pharyngeal-anastomoses-pylorus orient to the line of gravity, and it facilitates the passage of the food bolus into the duodenum after surgery. Hence, we believe the crucial factor determining early gastric emptying after esophageal surgery is gravity align-

ment, not gastric conduit movement.

Despite serial emptying studies justifying the feasibility of early oral intake of liquid food, it cannot fully fulfill the quality-of-life improvement requirement. Dining should be a feast for the eyes as well as the tastebuds. As we all know, repetitive chewing can turn solid food into a liquid bolus, and given that, we proposed the so-called "50 chews per bite", head rotation and chin-down posture as swallow facilitation strategies. We examined these strategies in 95 patients and proved that resuming soft semi-solid food oral intake on POD 2 "at will" was feasible, which drastically improved the PROs^[26].

When the issue of early oral intake of solid food is settled, the resected esophagogastric cancer patients can stay away from physical and psychological complications of the nasogastric tube (NGT), the nasojejunal tube (NJT) placement, or the feeding jejunostomy. Furthermore, the conventional postoperative draining management bears multiple tubes in the thoracic and cervical fields, often leading to postoperative pain or an ambulation barrier. We invented a thin (5mm in diameter), soft, and multi-functional draining system through the posterior mediastinum and transhiatus, covering the cervical, thoracic, and abdominal fields. Our experiment, including 78 cases, indicates the novel draining system is feasible and safe^[7].

To meet the requirements of sustainable ERAS program development, our innovation processes go beyond optimization, retrofitting, and redesign based on incremental improvement, instead on breakthrough innovations. As of now, the goals of decreasing anastomotic leakage rate, patients getting rid of NGT, NJT, feeding jejunostomy, or multiple draining tubes, resuming oral intake food "at will," discharging within a week after surgery, PROs improvement, decreasing hospital stay and healthcare expense, are all achieved due to our NTNF mode^[6,20].

The perspectives of barriers and enablers in implementing the NTNF-ERAS program

Most esophageal cancer patients are elderly, frail, malnourished, and heavily morbid, as well as with relatively sophisticated anatomic adjacency and unpredictable lymph node metastases patterns. Thus, the scope of esophageal surgery encompasses radical resections of the primary tumor, systemic lymphadenectomy, and the reconstruction of the upper gastrointestinal tract, which will inevitably exacerbate overall systemic health status of the patients. The more radical surgery is performed, the greater trauma and risk patients will encounter. “Live longer” and “Live better” is sometimes a paradox. How to appropriately balance them is the ultimate goal for surgeons. The necessary conditions to achieve it are diligence and innovation in surgical strategies, techniques, and approaches.

Regarding perioperative safety, the advances in esophageal surgery have lingered between exploration and compromise. After a decade of technical improvements, the esophageal cancer NTNF-ERAS system has achieved a comprehensive and mature level^[27], suitable for all surgical candidates. It has become a standard pathway in our daily practice.

Over the past two decades, esophageal surgery in China has experienced a stage-by-stage transition from left-sided to right-sided thoracotomy, from open thoracotomy to minimally invasive surgery, and from direct surgery to multimodality treatment. The NTNF-ERAS system incorporating novel technologies and modalities has allowed esophageal surgery to reach new heights. The iterative development process will embrace the emerging concepts, technologies, devices, and drugs to perfect the NTNF-ERAS system.

With the development of multimodality treatment and the advent of novel agents, esophageal surgery produces more prolonged survival, and the better quality of life is then inevitably expected. Currently, patients usually face the clinical sequelae of irritating

cough, arrhythmia, distension, chronic diarrhea, dyspepsia, or weight loss, which may be related to vagal denervation. Meanwhile, the clinical complete response is achievable when treating selective early-stage esophageal cancer via endoscopic submucosal dissection (ESD) followed by chemoradiation or definitive chemoradiation, challenging the current surgical modalities. For this reason, it is necessary to stage esophageal cancer accurately to choose the optimal therapeutic approach based on the available options, from organ preservation strategies to demolitive surgery. In addition, the role of lymphadenectomy in long-term survival improvement for locally advanced esophageal cancer is warranted in a larger Chinese cohort; the necessity and efficacy of lymphadenectomy for early-stage esophageal cancer (pT1b) after ESD continues to come up as a red flag.

Conclusions

In our view, we should continue to pursue customizing approaches for an individual esophageal cancer patient and to enable organ preservation with focusing on the maintenance of function in the future, with respect to the principles of tumor biology. In so doing, we will acquire experience in blurring the surgical boundary between the limit and the limitless of technology. These are welcome advances, and one would only need more detailed data and cooperative efforts to develop a novel function preservation ERAS system for esophageal cancer patients.

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