Editorial

The first randomized controlled trial on early versus late oral feeding after minimally invasive esophagectomy and the ongoing quest for more evidence

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Since many years, the question about how to deal with postoperative feeding after esophageal resection has become an important topic of debate.

Questions such as: what is your policy regarding postoperative feeding? [or leaving a nasogastric tube (NT), or using a jejunostomy for feeding], are repeatedly asked during surgical meetings. The answers by the speakers are equally divided between taking a conservative posture (waiting to start with oral feeding) and the progressive ones that show a tendency to initiate oral feeding as early as possible and not leaving a NT after the operation.

The general fear involved is commonly the anastomotic leakage triggered by early feeding and resulting consequences as abscesses and mediastinitis.

However, evidence about when to initiate the oral feeding after esophageal resection is clearly less available than in other disciplines of Surgical Digestive Oncology. For instance, after colorectal surgery during which the so-called fast track policy is nowadays generally adopted and used in favor of not leaving any postoperative NT and to initiate early oral feeding and active mobilization directly followed an operation.

Sun *et al.*, in a previous study compared two cohorts of 65 patients regarding early and late oral feeding, and found that an early oral feeding of patients after thoracolaparoscopic esophagectomy was feasible and safe. Moreover, the gastric emptying for liquid food after esophagectomy was significantly faster in the early oral feeding group (1).

Advantages holding for early oral feeding, such as less postoperative stress, quicker recovery of the function of the digestive tract, better immunological preservation, better quality of life (QoL) and short hospital stay, are frequently described. Yet, more evidence for these findings is deemed necessary.

Therefore, the paper published recently by Sun *et al.*, of the Department of Thoracic Surgery in Zhengzhou, China, in the *Annals of Surgery* about early oral feeding versus late oral feeding after esophageal resection is remarkably important (2).

They have performed an open-label, non-inferiority randomized control trial (RCT) in which they compared the early postoperative oral feeding (EOF) versus the late postoperative oral feeding (LOF) in two groups of 140 patients. All patients underwent a three stage McKeown minimally invasive esophagectomy (MIE). In a period of one and half years, 280 patients were enrolled in the study out of a total of 396 patients being assessed for eligibility during the same period of time.

Early oral feeding implies the no leaving of a NT or of a jejunostomy for feeding after intervention, initiating the oral feeding at postoperative day one (POD1). The feeding was steadily increased up to POD4 and daily supplemented by parenteral feeding to complete postoperative nutrition requirements and according to calculation by Harris-

Benedict formula. At POD4, parenteral nutrition was stopped unless problems had ensued with the nutrition requirements. In case of aspiration or anastomotic leakage, the oral feeding was halted.

The other group (LOF) of 140 patients were treated by nil by mouth up to POD7 by receiving a NT, postoperatively introduced by intervention radiology on POD1, and use for daily feeding up to POD7 when the NT was removed and the oral feeding was started (as in the EOF group according to the dietician guidance). In both groups there were some dropout patients, including those with direct complications, bronchoaspiration, and failure to undergo feeding tube placement or its dislocation. Final analysis was performed by intention to treat analysis, including 140 patients in every arm.

The first goal of this non-inferiority study was to determine if there were differences in Cardio-Respiratory-Gastrointestinal (CRG) postoperative complications during hospital stay, being the secondary outcomes the bowel function recovery and the short-term QoL. Score of Postoperative complications was done according to Clavien-Dindo classification. Regarding patients with two or more complications, only the highest grade was reported; while death and blood transfusions were reported separately. Also the need for ICU readmission, the need for NG tube insertion and readmission within 30 days were separately recorded.

Sample size and power of the study was accordingly calculated and based on the primary outcome. CRG complication rate was assumed to be 23% according to a previous study of the authors (1). The non-inferior margin was set at 13%, meaning that when the upper limit of the 95% confidence interval for the estimated difference in the postoperative CRG complication rate between the early oral feeding and the control (late feeding) group exceeded 13%, that then the EOF group would be inferior to the control group. Considering the dropout rate, a total of 280 patients had been the planned for enrollment in this study.

Only 1/3 of the patients underwent neoadjuvant therapy. The study was not performed blind. Basic characteristics of patients and clinical data are comparable.

All the patients underwent McKeown MIE with two- or three-field mediastinal lymphadenectomy dissection with a gastric tube of four cm, with no gastric emptying procedure followed by an embedded three-layer manual cervical anastomosis described previously by the authors.

Special attention was paid to the functioning of the vocal cords in all patients (laryngoscopy at POD1) and the early oral feeding was initiated very gently in the EOF group in order to avoid any bronchoaspiration. Furthermore, most patients could tolerate the EOF regimen; while only twelve patients in the EOF group were unable to receive or needing a discontinuation of the EOF regimen because of postoperative complications or symptoms of aspiration.

Concerning the outcomes of this study, no differences between the two groups were found concerning CRG or anastomosis site complications. EOF was non-inferior to LOF for CRG complications (30.0% in the EOF group versus 32.9% in the LOF group). Interesting to note is that the respiratory complications were less in the EOF group than in the LOF group (22.1% *vs.* 28.6%), as the pneumonia rates in both groups being comparable, 10.7% of the EOF and 12.1% of the LOF respectively. Anastomotic leak was not different in both groups, 3.6% in the EOF and 4.3% in LOF group respectively, being the unilateral vocal cord palsy 10.0% and 10.7% respectively. Intensive care readmission was 3.6% in the EOF and 6.4% in the LOF respectively. Moreover, compared with the LOF group, the EOF group showed significantly shorter time to first flatus and bowel movement indicating that early oral feeding was associated with early recovery of gut function.

Furthermore, at two weeks after operation, the patients in the EOF group reported significantly higher global QoL, but also a better physical, emotional and social function as well compared to the LOF group of patients. Also, the EOF group had lower symptom scores, such as fatigue, nausea and vomiting, pain, diarrhea, eating difficulties, appetite loss, dysphagia and trouble swallowing saliva as compared to the patients in the LOF group. Four weeks after operation, the patients of the EOF group reported higher global QoL and fewer symptoms of nausea, vomiting and diarrhea.

This study showed that allowing patients to slowly and carefully consume liquids and food immediately after McKeown MIE was non-inferior to the standard regimen of nil by mouth and enteral feeding for six days in terms of CRG complications.

This study is important. Concerning the first and second aims of the protocol, the importance of this study can now be determined.

The sample size was well calculated and the selected patients for inclusion and exclusion were well documented. The early oral feeding was carefully planned and performed. Moreover, after operation exclusion for early feeding was carefully done.

Therefore, it is our conviction that it might not be justified to practice oral intake restriction for fear of

anastomosis dehiscence and pneumonia after McKeown MIE resection.

From now on, it will be very difficult in daily practice not to adopt the principles found in this study.

Questions continue to arise of what will be the policy in open esophageal resections or after minimally invasive Ivor Lewis intervention with intrathoracic anastomosis. This is because in the western world, an increasing number of distal and junction esophageal adenocarcinomas are operated by this Ivor Lewis procedure. A Dutch study by Berkelmans *et al.*, has proposed the Nutrient II trial, a RCT comparing two groups of patients who underwent a total or hybrid minimally invasive Ivor Lewis procedure, a direct oral feeding versus a delayed oral feeding, being the primary outcome measure the functional recovery and being the secondary outcomes the surgical complications, nutritional status, reinterventions and QoL (3). This study is based on a previous performed study by Weijs *et al.*, on 50 patients undergoing MIE, its majority with intrathoracic anastomosis, and having compared this with a cohort of another 50 patients with delayed oral feeding (4). They concluded that immediate start of oral nutrition following intrathoracic anastomosis after esophagectomy seems to be feasible and does not increase complications as compared to a retrospective study and literature.

In conclusion, the remarkable study of Sun *et al.*, signified by its quality as CRT, serves as a new important step to adopt early oral feeding in patients who underwent a McKeown MIE esophagectomy.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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