Routine post-operative supplemental nutrition: A Randomized Controlled Trial

Protocol 01

06/16/2014

A. STUDY AIMS

Specific Aim 1: To determine if routine dietary supplementation with enteral tube feeding affects recovery and quality of life after esophagectomy. Medicare rules only pay for enteral supplements (tube feeding) if the patient needs alternative feeding for greater than 3 months. Many insurers have adopted these rules, without evidence in post-operative patients.

- We hypothesize that routine post-operative supplementation will enhance patients recovery and quality of life, by increasing the time of adequate nutrition.

Specific Aim 2: To determine the occurrence of common complications and readmissions post-operatively between patients who are routinely discharged with tube feeding and those that are not. If patients are not discharged with tube feeds, they must obtain all of their nutrition by mouth, which may be difficult in the early post-operative period.

- We hypothesize that routine use of tube feeding may reduce the occurrence of complications.

The <u>secondary aims</u> of this randomized clinical trial are:

- To compare costs of care between groups.
- To assess how length of stay (LOS) and readmission rates are affected by routine use of tube feeding, as well as costs of care.
- Rates of occurrence of tube feeding or jejunal tube-specific complications

B. BACKGROUND AND SIGNIFICANCE

Nutritional support is taking on an increasing focus in peri-operative surgical care. It is particularly important in esophageal resection, which is a high-risk operation in a patient population whose pre-operative condition may be reduced due to pre-operative chemo- and radio-therapy, as well as dysphagia from the cancer. Post-operatively, patients are routinely cleared to take nutrition by mouth once an esophagram is done post-operative day 7 and shows no abnormality.

Tube feeding should be at goal by day 7, but is discontinued once patients are discharged, as long as they are able to eat, i.e., do not have evidence of anastomotic leak or other serious complications. The amount patients are able to eat is frequently variable, and is not well recorded prior to or after discharge. There may be a dip in calories consumed, which if severe, will lead to readmission for

hydration, failure to thrive, or possibly the development of a post-operative complication.

Currently all patients are discharged with the jejunal feeding tube placed at the operation, just in case they are unable to eat post-operatively due to an unforeseen complication. Since many insurers and Medicare require patients to pay for tube feeding needed for less than three months (~$800/month and up, plus the services of a home health nurse), we do not routinely require patients use the feeding tube once discharged.

For esophagectomy specifically, and upper gastro-intestinal surgery in general, there is very limited literature looking at this question. Small randomized studies have not shown a benefit to routine tube feeding, although the numbers were very small, ranging from 12 to 70 in each group. Furthermore, the duration of tube feeding averaged 14 days, and even in the groups being fed enterally, were not meeting caloric needs in the period studied.

C. STUDY SCHEMA

Patients will be evaluated for surgery by the study surgeons. Patients scheduled to undergo an elective esophagectomy and who meet inclusion criteria (See Section E.1) will be approached for enrollment. Written informed consent will be obtained from all enrolled patients (see Appendix B). Pre-operative Quality of Life Survey will be obtained using the EORTC QLQ-C30 (see attached). Patients will then be randomly assigned to either routine post-operative tube feeding for 1 month, or usual practice, tube feeding to continue in the hospital until the patient is taking adequate nutrition by mouth at POD#8, or upon discharge. Since this study cannot be blinded, patients that cannot take nutrition by mouth at POD#8, or are tube feeding dependent on discharge will not be included in analysis.

Figure 1. Illustrates the study design

D. OUTCOME MEASURES

The primary outcome measure for specific aim 1 will be the quality of life and patient satisfaction as measured by post-operative survey instruments.

Secondary Outcomes for specific aim 1:

- Complications following surgery (jejunal tube)
- Length of stay
- Costs

The primary outcome for specific aim 2 will be the occurrence of post-operative complications such as: atrial fibrillation, delirium, anastomotic leak, pneumonia within the 30-day post-operative time frame.

Secondary Outcomes for specific aim 2:

- Readmission rates and costs of care.

E. STUDY POPULATION

The study population will consist of patients who are recommended to undergo an elective esophagectomy as determined by the surgeon's evaluation.

E.1. Inclusion Criteria

E.1.1 Undergoing an elective esophagectomy
E.1.2 jejunal feeding tube placed at the time of surgery

E.2. Exclusion Criteria

E.2.1 Emergent procedure.
E.2.2 Less than 18 years of age.
E.2.3 Inability to provide informed consent or to complete testing or data collection.
E.2.4 Unwillingness to be randomized.
E.2.5 Tube feeding dependent on discharge.

F. RANDOMIZATION AND MASKING

Randomization envelopes will be created at the start of the study. Each envelope will be opened prior to discharge or at POD#8 if patients are able to take adequate nutrition by mouth, to determine if post-operative tube feeding will be continued or not.

By consenting to the study, patients agree to continue tube feeding for at least 50% of caloric needs for 1 month post-operatively. Cross-over after randomization will be permitted for patient condition, although once randomized, patients will be analyzed by the original group.

- A copy of the signed research consent form must be included in the patient's hospital chart.

G. TREATMENTS

G.1 Standardization of Intervention

All Procedures:

1. The participating study surgeons have been trained in and regularly perform esophagectomies with jejunostomy tube placement.
2. The supervising study surgeon will be present for key portions of the procedure. Residents or fellows may participate in procedures as is standard.

3. Patients will undergo standardized preoperative and postoperative education.
4. Patients will undergo standard postoperative care specific to the procedure performed, including enteral tube feeding while in the hospital until adequate nutrition by mouth is tolerated.

Standardization of Postoperative Care
Standard protocols will apply while patients are admitted to the hospital. Once discharged from the hospital, patients will be evaluated at a routine postoperative appointment. Attending providers will be blinded as much as possible to the discharge tube feeding regimen.

H. MEASUREMENT

The assessment instruments that will be used for specific aim 1:
1. EORTC QLQ-C30, Quality of life in cancer patients

The complications assessment instruments that will be used for specific aim 2:
1. HUM00012731 data collected around the time of operation and post-operative visit.
2. Long-term data from HUM00012731

Patients will also be invited to enroll in the "Patient outcomes following esophagectomy for benign and malignant disease" HUM00012731, a study in which the PI (Philip Carrott) is also a co-investigator. To minimize patient burden, the baseline preoperative assessment and the evaluation for quality of life will be performed according to the protocol outlined in HUM00012731. Demographics and history forms HUM00012731 will only be administered once preoperatively. This data will then be shared to support the study aims of this protocol to minimize patient inconvenience. In the event, that a patient does not wish to be co-enrolled in HUM00012731, the attached forms (EORTC QLQ-C30 and Demographics and history forms HUM00012731) will be administered by the Thoracic Surgery Clinical Coordinator, who will be trained and added to the HUM000XXXXX study protocol, at the scheduled time points outlined in Section N.

H.1 Primary Outcome Measures:

a. Specific Aim 1
Quality of life data will be assessed pre-operatively and at the post-operative visit.

b. Specific Aim 2

Occurrence and severity of complications will be recorded by HUM00012731. Patients will be assessed at discharge and return visits. Adverse events following surgery (e.g., pneumonia, DVT, PE, anastomotic leak, atrial fibrillation, delirium, etc.) will be identified prospectively by the study team

H.2 Secondary Outcome Measures

a. Specific Aims 1&2

1. Jejunostomy tube-specific complications will also be identified prospectively. J-tube specific complications include infection, bowel obstruction that may require surgical repair, discomfort, diarrhea and dumping syndrome.

2. Other outcome measures (length of stay, readmission, etc.)

3. **Costs** will be determined retrospectively by reviewing the administrative billing data.

H.3 Schedule of Measurements

Section N details the schedule of measurements. Data will be collected preoperatively at the initial screening visit, during the perioperative period, at the follow-up appointment (2 weeks following discharge), and at 1 month, 3 months, and 6 months (by telephone or mail).

I. DATA COLLECTION

All data collection following surgery will be performed by research staff other than the study surgeon. This will reduce bias by maintaining masking in data collection of outcome measures. All research staff will be trained and certified to perform data collection procedures. Allowable windows for timed evaluations are specified in Section N and include a one-week window on each side of the postoperative visit planned at 2-3 weeks. The assessments at 1-month, 3-months, and 6-months will take place by mail and will not require a visit to the clinical site.

I.1 Demographics, Medical History, and Physical Examination

a. History

i. Age
ii. Sex

iii. Previous medical history
iv. Prior thoracic procedures
v. Primary diagnosis
vi. Previous thoracic chemotherapy or radiation
vii. Planned procedure
viii. Comorbidities will be collected using the Charlson Comorbidity index collected at baseline

b. Physical Examination

i. Height
ii. Weight
iii. BMI

J. STATISTICAL AND DATA MANAGEMENT CONSIDERATIONS

For the specific aims:

Specific Aim 1: Quality of Life measurements will be compared at 6 months, using descriptive statistics.

Specific Aim 2: Calories will be compared between groups.

For the secondary aims: Height and weight will be compared between groups at 30 days and 6 months.

Sample size justification: This was measured with the possible recruitment pool and differences between groups.

Interim analysis: At 50% recruitment or three years.

Randomization:

This study will randomize eligible patients to receive post-operative tube feeding for 1 month or standard post-operative care in a one-to-one fashion. Patients will be randomized using a blocked randomization technique in order to ensure equal sample sizes across groups. Lili – is this correct? The study statistician (Lili Zhao) will generate the randomization assignment table for the study's data manager. The investigators will call the data manager for the treatment assignment when a patient has been fully consented and is determined to be eligible for study enrollment.

K. RECRUITMENT

An estimated sample size of XXXXX – insert from Lili evaluable* patients will be enrolled over a period of 12-24 months.

* Patients that meet inclusion criteria (see section E.1) and are not excluded from participation in the study by the exclusion criteria (see section E.2). If there are patients who drop out of the study or are loss to follow-up, they will be replaced to achieve a minimum sample size of XXXXX – insert from Lili evaluable patients for specific aims 1 and 2.

ETHICAL CONCERNS- INFORMED CONSENT

It is unclear what kind of difference tube feeding may make post-operatively, which is why we are doing this study. Previous small studies have not shown any short-term differences. (see APPENDIX B).

L. DISCUSSION OF POTENTIAL LIMITATIONS IN STUDY DESIGN

A potential pitfall is that patients who consent to the study in the preoperatively, may not continue to meet eligibility criteria prior to discharge or at POD#8 because they are not able to take adequate nutrition by mouth, thus excluding the patient from randomization and further participation in the trial.

Another potential pitfall is that patients who randomize to have their tube feeding discontinued at discharge may (due to patient condition) require tube feedings to be resumed to supplement nutritional needs. Cross-over after randomization will be permitted for patient condition, although once randomized, patients will be analyzed by the original group.

Lili, how do we construct randomization schema and power analysis to account for these limitations?

N. TIMELINE OF VISITS, MEASURES AND FORMS:

Table 1 Timeline of Visits and Data Collection

	Screening & Enrollment	Inpatient (post-op)	Follow-up (Clinic- 2 weeks)	1 Month	3 Months	6 Months	Specific Aim (1 or 2)
Eligibility	**X**	**X***					**1/2**

Consent	**X**						**1/2**
Demographics	**X**						**1/2**
Charlson Comorbidity Index	**X**						**1/2**
Quality of Life Assessment	**X**		**X**	**X**	**X**	**X**	**1**
Randomization		**X**					
Adverse Events			**X**	**X**	**X**	**X**	**2**
Hospital LOS			**X**				**1/2**
Costs						**X**	**1/2**

*assess for continued study eligibility prior to randomization

O. RESEARCH COSTS

Costs incurred by the study will be borne by unrestricted Section of Thoracic Surgery research funds. Only those patients with insurance that does not cover the post-operative tube feeding will be paid for by the Section of Thoracic Surgery. There are no costs for data collection that will be charged to the patient.

P. REFERENCES CITED

Early enteral feeding compared with parenteral nutrition after oesophageal or oesophagogastric resection and reconstruction.
Gabor S, Renner H, Matzi V, Ratzenhofer B, Lindenmann J, Sankin O, Pinter H, Maier A, Smolle J, Smolle-Jüttner FM.
Br J Nutr. 2005 Apr;93(4):509-13.
PMID: 15946413

Fit for surgery: an expert panel review on optmising patients prior to surgery, with a particular focus on nutrition.
Windsor A, Braga M, Martindale R, Buenos R, Tepaske R, Kraehenbuehl L, Weimann A.
Surgeon. 2004 Dec;2(6):315-9. Review.
PMID: 15712570

Immunonutrition in patients undergoing esophageal cancer resection.
Mudge L, Isenring E, Jamieson GG.
Dis Esophagus. 2011 Apr;24(3):160-5. doi: 10.1111/j.1442-2050.2010.01117.x. Epub 2010 Oct 13. Review.
PMID: 20946133

An evidence-based approach to perioperative nutrition support in the elective surgery patient.
Miller KR, Wischmeyer PE, Taylor B, McClave SA.
JPEN J Parenter Enteral Nutr. 2013 Sep;37(5 Suppl):39S-50S. doi: 10.1177/0148607113493928.
PMID: 24009248

Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial.
Ryan AM, Reynolds JV, Healy L, Byrne M, Moore J, Brannelly N, McHugh A, McCormack D, Flood P.
Ann Surg. 2009 Mar;249(3):355-63. doi: 10.1097/SLA.0b013e31819a4789.
PMID: 19247018

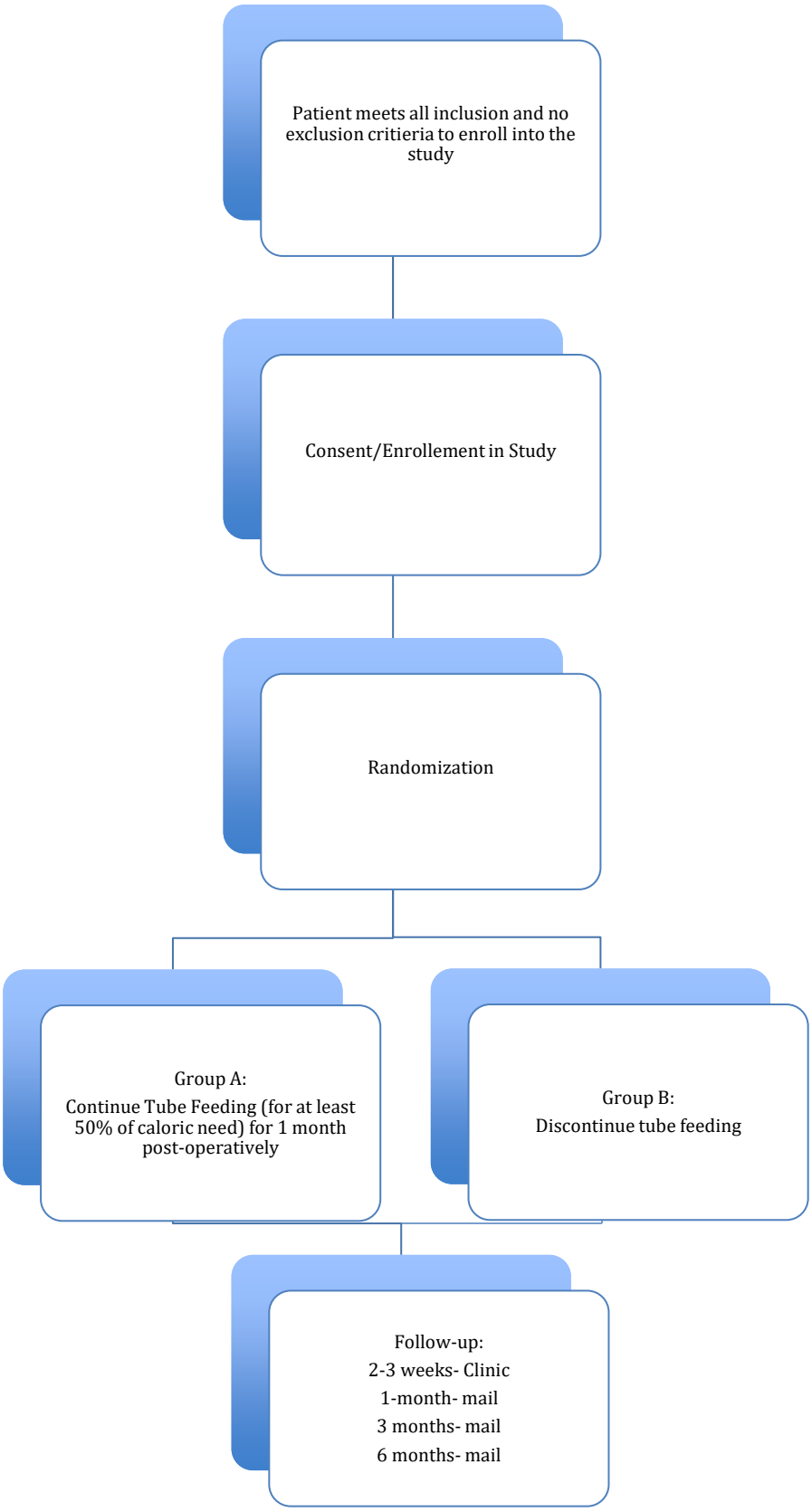

Figure 1 Study Design