

Expedite recovery from esophagectomy and reconstruction for esophageal squamous cell carcinoma after perioperative management protocol reinvention

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Background: Surgery for esophageal cancer is invasive and challenging, and always to be followed with arduous post-operative care and recovery. This study, maybe one of the first in Asian populations, is to determine whether a reinvented protocol for perioperative management for esophageal cancer surgery which is being implemented in our department, will lead to a faster convalescence and also significantly decrease financial burdens garnered by patients during hospitalization.

Methods: Operated on by the same surgeon and team in the same hospital, consecutive patients who had received esophagectomy and reconstruction for esophageal squamous cell carcinoma were retrospectively reviewed. On the basis of two different treatment periods, patients were divided into two groups: A and B. Group A was patients who had received the new reinvented protocol between 2012 and 2016, while group B patients were those having received the previous protocol between 2008 and 2011. Their demographics, post-operative outcome, and hospital charges were collected and compared.

Results: There were 64 patients in group A, and 69 in group B. Ventilator days ($P < 0.001$), ICU stay ($P < 0.001$), and post-operative stay ($P < 0.001$) were significantly shorter in group A patients. Complication rates were similar between the two groups. No hospital mortality was noted in either group. Hospital charges in group A were found to be perceptively lower, although not statistically significant (P value = 0.078).

Conclusions: The current protocol of perioperative care effectively ameliorated convalescence after esophagectomy and reconstruction for esophageal squamous cell carcinoma without increasing complication rate or mortality. It is also potentially more practical in future health care policies during this era of financial shortage.

Keywords: Recovery; perioperative management; esophagectomy; esophageal squamous cell carcinoma

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Introduction

Cancer is the leading cause of death in Taiwan, and esophageal cancer is ranked number nine among them. There were 2,496 new cases, of which 754 received resection in 2013 (1).

Radical resection and reconstruction for esophageal cancer carry certain risks. The operative time is relatively long; it is also associated with high morbidity. In addition to this, the post-operative course is strenuous, owing to possible respiratory complications, anastomotic leakage, and poor nutritional status. Consequently, hospital stay after surgical treatment for esophageal cancer is often long, leading not only to increased financial burden, but also late return to normal life.

Thus Kehlet and Wilmore's research in 2002 (2) provided a basis for our study. They introduced a fast-track surgery pathway in order to advance post-operative surgical care, with positive results including post-operative recovery enhancement, reduction of patients' physiological and psychological stress, and decrease in length of hospital stay (2,3).

As we know, the reduction of hospital expenditure is currently a primary focus for policy on a worldwide scale due to increasing requisite and shortage of resources. With this in mind, how we advance the convalescence of post-esophagectomy patients is an imperative and important issue in all medical centers.

Confident in our mature surgical dexterity, experienced anesthesiology technique and well-trained postoperative care team, in 2012, we reinvented our old protocol for improvement of postoperative recovery of patients who received esophagectomy and reconstruction for esophageal squamous cell carcinoma after detailed interdisciplinary discussions and meetings (*Table 1*). Video-assisted thoracic surgery (VATS) esophagectomy was also adopted as we have been implementing VATS for pulmonary surgery since 2006. This study is to determine whether the new protocol led to an improvement of patient recovery, including complications, mortality, hospital stay, and financial burden.

Methods

This is a retrospective study. Patients with esophageal squamous cell carcinoma who had received esophagectomy and reconstruction with stomach were reviewed. Data from two groups of patients, categorized according to their treatment period, were collected. Group A patients

were cared for according to the recently adopted protocol, starting from January 2012. Up to June 2016, 64 patients were collected. Group B was a group of 69 patients who had been placed on the old protocol between January 2008 and December 2011. All patients had suffered from esophageal squamous cell carcinoma. They all received esophagectomy through thoracotomy or VATS, reconstruction with stomach through laparotomy and feeding jejunostomy. There was no case where the colon was used as an esophageal substitute. Patients' demographic data and pre-operative ECOG (Eastern Cooperative Oncology Group), tumor location, clinical stage, pathologic stage, pre-operative treatment modality, length of post-operative stay, days in ICU, post-operative ventilator days, operative time, intraoperative blood loss, intraoperative blood transfusions, dissected three-field lymph nodes, complications, 30-day hospital mortality, and medical charges were recorded (*Tables 2 and 3*).

Cessation of smoking for all patients for at least two weeks before operation was mandatory.

All data was obtained as part of routine clinical care from charts so that extra patient consent was waived. The study was approved by IRB [KMUH-IRB-E(II)-20150240].

All clinical and pathologic staging were determined according to the criteria of the 7th Edition of the AJCC cancer staging manual (4).

Surgical procedure

- (I) Hybrid (H)—VATS esophagectomy and Laparotomy reconstruction with stomach.
Patients in Group A were operated on with Hybrid procedure. Twenty-nine point seven percent were converted into thoracotomy esophagectomy owing to severe local tumor adhesions after pre-operative concomitant chemoradiotherapy (CCRT).
- (II) Conventional procedure—thoracotomy esophagectomy + laparotomy for stomach tube.
All group B patients received the conventional procedure.

Operative technique

Abdominal procedure

Median laparotomy was made, followed by mobilization of the entire great curvature of the stomach to preserve the right gastroepiploic artery as the pedicle. The short and left gastric vessels were divided. The abdominal esophagus was transected. The gastric conduit was made by stapling the lesser

Table 1 Clinical protocol for traditional and reinvented group

POD	Traditional group	Reinvented group
0	To ICU with endotracheal tube Ventilator with sedation	Extubation in operating room Direct transfer from OR to ICU Start incentive spirometry at ICU NPO with IV fluid, NG decompression, albumin IV supply, PCA Respiratory care by therapists
1	Wean off ventilator Extubate early next morning TPN Bed rest	Start strolling at ICU Pulmonary toilet, incentive spirometry TPN, NG drainage Transfer to ward if chest radiography, vital signs and O ₂ saturation stable Ambling in ward
2	Pulmonary toilet Incentive spirometry Transfer to ward if stable	TPN NPO Incentive spirometry Neck wound open care Keep mobilization
3	Try walking the next day Chest care	Remove neck drainage, neck wound open care Stimulant laxatives Start jejunostomy feeding with N/S Remove urinary catheter
4	Remove neck J-P drain	Start jejunostomy feeding with milk TPN tapered off and stopped NG clamped
5	Laxative if no bowel movement	Increase jejunostomy feeding amount Remove abdominal and chest tube drain Remove CVC
6	Start jejunostomy feeding with N/S TPN tapered off CVC removed	Remove NG tube
7	Jejunostomy feeding with milk	Start drinking water Education
8	Remove abdominal drain	Discharged
9	Remove chest tube	
10	Clamp NG tube	
11	Remove NG tube	
12	Drink water	
13	Released	

POD, post-operative day; ICU, intensive care unit; TPN, total parenteral nutrition; J-P drain, Jackson-Pratt drain; N/S, normal saline; CVC, central venous catheter; NG, nasogastric tube; OR, operating room; NPO, nil per os; IV: intravenous; PCA, patient control analgesia.

Table 2 Demographic data for reinvented group (A) and traditional group (B)

Demographic data	2012–2016 (A)	2008–2011 (B)	P value [†]	P value [‡]
Number	64	69		
Age (years)	53.8±9.6	55.1±8.1	0.415	0.522
Gender, n (%)			0.682	
Male	62 (96.9)	65 (94.2)		
Female	2 (3.1)	4 (5.8)		
Location, n (%)			0.004	
U	16 (25.0)	8 (11.6)		
M	25 (39.1)	47 (68.1)		
M–L	5 (7.8)	1 (1.4)		
L	18 (28.1)	13 (18.8)		
Clinical stage			0.69	
I	9 (14.1)	11 (15.9)		
II	17 (26.6)	14 (20.3)		
III	38 (59.4)	44 (63.8)		
Pathologic stage, n (%)			0.199	
0	8 (12.5)	2 (2.9)		
I	17 (26.6)	21 (30.4)		
II	19 (29.7)	20 (29.0)		
III	20 (31.3)	26 (37.7)		
Pre-op CCRT (yes), n (%)	22 (34.4)	15 (21.7)	0.123	
ECOG =0, n (%)	6 (9.3)	2 (2.9)	0.153	
ECOG =1, n (%)	58 (90.7)	67 (97.1)		

U, upper; M, middle; M–L, middle-to-lower; L, lower; Pre-op CCRT, pre-operative concomitant chemoradiation; ECOG, Eastern Cooperative Oncology Group. [†], Student *t*-test for continuous data and Chi-square with Fisher's exact test for category data; [‡], non-parametric Mann-Whitney U test.

curvature and forming a gastric tube. Kocher's maneuver was performed when necessary. Abdominal lymphadenectomy and feeding jejunostomy were routinely performed.

Neck procedure

A 5-cm oblique incision was made over the anterior border of the left sternocleidomastoid muscle. The neck esophagus was mobilized to facilitate communication with the right chest. Left neck lymphadenectomy was also carried out with caution so not to injure the left recurrent laryngeal nerve. Gastric tube was pulled up through the substernal route. Cervical anastomoses were all conducted using hand-sewn interrupted mattress suture technique.

Thoracic procedure

The patients were placed in left lateral decubitus position. A right posterolateral thoracotomy incision was made. Mediastinal pleura were incised and the esophagus was separated from the adjacent mediastinal tissues and organs. The azygos venous arcade was routinely divided. Mediastinal lymphadenectomy was also performed. For VATS approach, utility of three 10-mm trocars were placed over fourth intercostal space, anterior axillary line; sixth intercostal space, anterior axillary line, and eighth intercostal space, posterior axillary line. The operative steps were performed in a similar fashion as open thoracotomy. The operative procedure had been shifted to thoracoscopic

Table 3 Short-term post-operative outcomes

Variables	2012–2016 (A)	2008–2011 (B)	P value [†]	P value [‡]
Operative procedure (H)	45 (70.3%)	0	<0.001	–
Operative procedure (C)	19 (29.7%)	69 (100%)	–	–
Ventilator (days)	0.1±0.4	1.3±2.7	<0.001	<0.001
ICU stay (days)	1.5±1.1	3.6±3.4	<0.001	<0.001
Post-operative stay (days)	9.5±2.6	14.6±6.8	<0.001	<0.001
Operative time (minutes)	340.0±54.1	344.8±52.3	0.605	0.510
Intraoperative blood loss (mL)	72.9±23.3	67.8±25.3	0.227	0.023
Intraoperative blood transfusions (yes)	1 (1.6%)	3 (4.3%)	0.620	–
Dissected three-field lymph nodes	35.1±15.5	25.4±11.6	<0.001	<0.001
Complication (yes)	11 (17.1%)	24 (34.8%)	0.300	–
Hospital charges (US \$)	7,299.9±1,085.1	8,937.2±3,808.6	0.078	0.149

H, hybrid; C, conventional. [†], Student *t*-test for continuous data and Chi-square with Fisher's exact test for category data; [‡], non-parametric Mann-Whitney U test.

esophagectomy in recent years owing to a worldwide trend of minimally invasive surgery (MIS).

Respiratory care protocol

Respiratory care was administered to patients receiving esophageal surgery by a respiratory therapist throughout the duration of hospitalization both in group A and B. Pre-operative assessment included incentive spirometry, abdominal breathing, and appropriate cough technique. Post-operative assessment included the above items, as well as optimization of oxygen delivery, inhalation medical therapy, and the process of weaning from mechanical ventilation if necessary.

About anesthesia

Pulmonary aspiration is a risk and should be minimized as much as possible with H₂ blocker or proton-pump inhibitor preoperatively. Awake nasogastric suctioning may also help.

Double-lumen endobronchial tube (Mallinckrodt Inc., St. Louis, MO, USA) was routine for both conventional and VATS esophagectomy.

Thoracic epidural analgesia was administered, as routine, for post-operative pain control.

Statistical methods

Descriptive statistics were compiled and all data was expressed

as mean ± standard deviation and number (percentage). Student *t*-test for continuous data and Chi-square with Fisher's exact test was used for category data to determine the difference between the two time-groups, year 2008–2011 and year 2012–2016. Additionally, non-parametric Mann-Whitney U test was also used to determine the difference of time variables, such as age, ICU stay in days, days on ventilator, days of post-operative stay, and operative time between the two time-groups. Statistical analyses were performed using SPSS 20 for Windows. All statistical tests were two-tailed and P value of <0.05 was considered as statistically significant.

Results

Demographic data is shown in *Table 2*, and short-term post-operative outcomes are shown in *Table 3*. Age (P=0.415), gender (P=0.682), pre-op CCRT (P=0.123) and ECOG (P=0.153) are determined to be of no statistical significance. The number of mid-third tumor in Group B was more than that of Group A. Group A showed significantly lower ventilator days (P<0.001), ICU stays (P<0.001), and post-operative stay (P<0.001) and more dissected three-field lymph nodes (P<0.001). Operative time, intra-operative blood loss and blood transfusions were statistically insignificant. There was no significant difference in complications rates between the two groups (P=0.300). Of them, pneumonia rate was

Table 4 Complications between reinvented group (A) and traditional group (B)

Complications	2012–2016 (A) (%)	2008–2011 (B) (%)	P value [†]
Number	11/64 (17.1)	24/69 (34.8)	
Pneumonia	4 (6.3)	9 (13.0)	0.352
Anastomotic leakage	2 (3.1)	4 (5.8)	
Respiratory failure	0	1 (1.4)	
Chylothorax	0	1 (1.4)	
Readmission	1 (1.6)	1 (1.4)	
Hoarseness	4 (6.3)	8 (11.6)	
30-day mortality	0	0	

[†], Chi-square with Fisher's exact test.

reduced from 13.0% to 6.3% and anastomotic leakage rate from 5.8% to 3.1%. No hospital mortality was recorded (*Table 4*). The hospital charges in Group A were perceptively less than that of Group B (*Table 3*), although P value (P=0.078) did not reach statistical significance.

Discussion

According to the results of our study, the implementation of our new perioperative management protocol for esophagectomy and reconstruction was safe and feasible. Notably, post-operative complications and mortality had not increased. This can be explained in the following discussion.

In Group A, with the exception of one patient, all were extubated successfully in the operating room. The one patient who kept his tube to ICU was a 74-year-old male with FEV₁: 1.11 L. He was slowly weaned off the ventilator and extubated during a 4-day stay in ICU. Only two patients were re-intubated owing to ineffective cough and profuse sputum. They were extubated the next day without any difficulty. In the past, surgeons were wary of early extubation, owing to fear of re-intubation in the event of respiratory fatigue and pain after major operation. Lack of round-the-clock experienced staff was a concern. The current concept of prolonged intubation is a risk factor for pneumonia and systemic inflammatory reaction (5). Whereas, early extubation may shorten or even avert intensive care stay (6), as well as circumvent the use of ventilation.

It must be noted, however, that uneventful anesthesia is a prerequisite for early extubation and smooth recovery. We were able to achieve this by carefully considering the following two factors. First, we utilized a fixed

anesthesiologist who was familiar with esophageal surgery, and integrated with our surgical team. Second, hemodynamic stability was maintained through optimal fluid management. Urinary output has formerly been the indicator of fluid adequacy, but new monitoring device such as stroke volume variation, if carefully used, bearing in mind that they are currently not without imperfection, could optimize perioperative perfusion, decrease incidence of post-operative lung edema, acute respiratory distress syndrome, and anastomotic leakage (7).

We routinely control post-operative pain with thoracic epidural analgesia. It has been shown to reduce the incidence of respiratory complications after surgery (5,8). Moreover, it improves graft microcirculation and prevents anastomotic insufficiency (9). A critical note is that the anesthesiologist should always stay at his or her post during the operation due to the unpredictable likelihood of arrhythmia and even hypotension that would occur during mediastinal dissection. Closed clear communication between the anesthesiologist and surgeon is essential. In some series, the ICU was bypassed, and the patients were transferred to the ward after close observation in post-anesthesia care unit (10). However, our philosophy was that all patients, stable or otherwise, although extubated, should be sent to ICU for immediate care. Despite the chances being low, we could not risk sudden aggravation. The total hospital stay would not be prolonged even if ICU stay was one or two days longer. The only disadvantage is higher cost.

All our patients started walking on the first postoperative day in Group A. As we know, early ambulation promotes circulation and improves peristalsis. It is advantageous for patients to return to enteral feeding as soon as possible (11) so that nutritions can be obtained alimentarily and side-

Table 5 Comparison of outcomes between VATS and open esophagectomy

Variables	2012–2016 (VATS)	2008–2011 (Open)	P value [†]	P value [‡]
Number	45	69	–	–
Ventilator (days)	0.1±0.5	1.3±2.7	0.001	<0.001
ICU stay (days)	1.4±0.9	3.6±3.4	<0.001	<0.001
Post-operative stay (days)	9.1±2.2	14.6±6.8	<0.001	<0.001
Complication (yes)	10 (22.2%)	24 (34.8%)	0.278	–
Operative time (minutes)	341.1±56.8	344.8±52.3	0.724	0.738
Intraoperative blood loss (mL)	72.9±24.0	67.8±25.3	0.289	0.057
Intraoperative blood transfusions (yes)	0	3 (4.3%)	0.277	–
Dissected three-field lymph nodes	35.5±15.6	25.4±11.6	<0.001	<0.001

[†], Student t-test for continuous data and Chi-square with Fisher's exact test for category data; [‡], non-parametric Mann-Whitney U test.

effects of total parenteral nutrition lessened.

Bronchofiberscopic pulmonary toilet is a routine procedure on the first postoperative day in Group A. Most patients had the problem of effective cough, so pulmonary infection was a potential hazard. Compared with the literature (12–14), our pneumonia rate was much lower than expected.

It is worth mentioning that we encouraged families to come into the ICU and help patients to walk around while they were waiting to be transferred to ward throughout the group A and B. This not only decreased the load on nursing staff, but also allowed patients to reunite with their family much sooner.

Another factor contributing to the short hospital stay is our low anastomotic leakage rate.

Anastomotic leakage would potentially extend the hospital stay for more than a week. Due to the refinement of operative technique in reducing anastomotic leakage, as we had described previously (15), the rate of anastomotic leakage was only 3.1% compared with the rate reported in the literature of approximately 10–15% (12–14). Handling the stomach gently and preserving as many collaterals as possible is the key. We have to emphasize that we did all our cervical anastomoses with hand-sewn technique, and the leakage rate was even lower than the reported rate by stapler method (16,17).

Postoperatively, we kept our patients NPO (nil per os) for six days instead of starting partake on the day after operation (18). Nutrition is through jejunostomy enterally.

First, we believe the healing of anastomosis will be more secure. Second, which was not mentioned in most of the

literature, is that a certain number of patients would choke during first swallowing after the operation. This would cause aspiration if patients were too weak to cough up. That is why we let our patients drink several days later, giving them sufficient time to gradually recuperate, and greatly reducing the possibility of aspiration. With regard to the problem of NG tube removal, we decided on the delay after early removal prompted incidences of vomiting. The patients started drinking on the next day to confirm that they had no swallowing difficulty or choking. After discharge, if swallowing was smooth, they were encouraged to try soft diet. All patients were followed-up at outpatient clinic. Nutritional status of course gradually improved with soft diet and even common diet. One thing we have to mention is that there was only one re-admission in the new protocol group, and this was not related to swallowing. Our protocol appears more conservative than others found in the literature, but patient recovery is comparable, with lower than reported complication rate.

Respiratory complication (6.3%) was also low in our series, attributed to the help of respiratory therapists. One thing we should admit is that the implementation of VATS esophagectomy—a MIS—in the last four years maybe one of the reasons for this improvement. As we know, VATS may decrease the rate of pulmonary complication and length of stay (19–21). In our series, we cannot say whether our current results are affected by this, and further research is required in this area. In particular, we also made comparison between VATS in Group A and open esophagectomy in Group B (Table 5). Similar to Table 3, the VATS-based Group A showed comparable result with significantly lower

ventilator days ($P < 0.001$), ICU stays ($P < 0.001$), and post-operative stay ($P < 0.001$). Besides, the result yielded no statistic significance with regard to operative time, intra-operative blood loss, and intra-operative blood transfusions. But there were significantly more dissected three-field lymph nodes in Group A ($P < 0.001$).

Moreover, according to the *Table 2*, patients in Group B seemed to be suffered from more advanced pathologic stage, less frequent use of CCRT and poorer ECOG, these cannot be precluded as factors causing better outcome of the Group A. But they are not statistically significant.

The hospital charges were conspicuously lower in Group A, although statistically insignificant. The difference was about US\$1,600 between the groups. It seems small of course, but it is currently the average two-month salary for an university graduate in Taiwan. This cost reduction is an encouraging news, probably related to the significant reduction of ventilator use, and ICU and hospital stay. We also note that hospital charges in Taiwan are tremendously low when compared with that of U.S. (14).

The strong point of this series is that we were able to minimize bias by drawing on the patients of the same one surgeon, in this single particular institute. Not only we do obviate the technical discrepancies that inherently exists among surgeons, but the facilities and policies that vary between institutions have also been kept constant. The limitations of this study are (I) case number still small; (II) the higher proportion of MIS in the last three years that may shorten the recent hospital stay; (III) the improvement of dexterity and growing of experience may abridge the post-operative stay year by year; (IV) quality of life has not been compared because of the lack of this information from the patients of Group B.

In conclusion, our result showed that newly-adopted reinvented perioperative management protocol for esophagectomy and reconstruction for esophageal squamous cell carcinoma is feasible, safe, and cost-effective. With the implementation of this protocol, the ICU days and post-operative days were shortened significantly without increasing complication and mortality. Meanwhile, the hospital charges were also reduced concomitantly.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: All data was obtained as part of routine clinical care from charts so that extra patient consent was waived. The study was approved by IRB [KMUH-IRB-E(II)-20150240].

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