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Achievements of perioperative assist team medical care in esophageal cancer surgery, Tokushima University Hospital

Seiya Inoue[1], Masakazu Goto[1], Satoshi Fujiwara[1], Takahiro Yoshida[1], Fuyumi Izaki[1], Taihei Takeuchi[1], Hiroyuki Sumitomo[1], Mariko Misaki[1], Hiroaki Toba[1], Hiromitsu Takizawa[1], Yasuhiro Hamada[2], Tetsuya Matsuura[3], Keiko Aota[4], and Hidenori Takano[5]

[1]Department of Thoracic, Endocrine Surgery and Oncology, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan, [2]Department of Therapeutic Nutrition, Institute of Health Bioscience, Tokushima University Graduate school, Tokushima, Japan, [3]Department of Rehabilitation Medicine, Tokushima University Hospital, Tokushima, Japan, [4]Department of Oral Medicine, Tokushima University Graduate school of Biomedical Sciences, Tokushima, Japan, [5]Department of Oral Management Center, Tokushima University Hospital, Tokushima, Japan

Abstract : Background : Radical esophagectomy is highly invasive and associated with many postoperative complications. A decline in postoperative QOL is a serious issue for patients, and comprehensive perioperative management through multidisciplinary cooperation is necessary. Our institution has established a perioperative assist team (OPERA) to address this need since 2017. Methods : This study included 109 patients with esophageal cancer who underwent neoadjuvant chemotherapy and esophagectomy from 2009 to 2018. O group, means OPERA intervention group, included 57 patients, and N group, means Non-OPERA intervention group, included 52 patients. The effects of the OPERA intervention on reducing chemotherapy-related adverse events and improving postoperative outcomes were retrospectively investigated. Results : The OPERA intervention significantly reduced the incidence of chemotherapy-related adverse events (P=0.002). In particular, anorexia and diarrhea, febrile neutropenia were significantly reduced (P<0.001, P=0.002, P=0.025, respectively). Postoperatively, the start date of walking was significantly earlier (P<0.001), the incidence of pneumonia was lower (P=0.022). At the time of postoperative discharge, N group was significantly greater weight loss compared to O group (P=0.002). The 5-year survival rate was longer in O group (P=0.003). Conclusion : The OPERA intervention reduced the incidence of chemotherapy-related adverse events and postoperative complications and helped improved prognosis. J. Med. Invest. 71 : 279-285, August, 2024

Keywords **:** *esophageal cancer, esophagectomy, perioperative assist team, postoperative complication*

INTRODUCTION

Radical surgery for esophageal cancer is the most invasive and difficult to perform among gastrointestinal surgical procedures, and is associated with a number of postoperative complications (1, 2). Many patients with esophageal cancer are elderly with multiple diseases, and those undergoing esophagectomy suffer from dysphagia, aspiration pneumonia, and decreased activity, resulting in a marked deterioration in QOL. Radical surgery for esophageal cancer requires comprehensive perioperative management based on multidisciplinary collaboration (3, 4).

In recent years, improvements in surgical techniques have enabled minimally invasive surgery using thoracoscopic or laparoscopic procedures. However, the prevalence of postoperative complications remains high (2, 5), and there is a need to improve not only surgical techniques but also perioperative management. Neoadjuvant chemotherapy (NAC) for advanced esophageal cancer is a standard approach, and multidisciplinary team interventions are necessary from the time of NAC. In this context, early intervention by a perioperative management team may help improve preoperative patient status and reduce postoperative complications (6, 7).

Received for publication February 15, 2024 ; accepted June 29, 2024.

Address correspondence and reprint requests to Seiya Inoue, M.D., Ph.D, Department of Thoracic, Endocrine Surgery and Oncology, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-7144. E-mail : inoue.seiya@tokushima-u.ac.jp

The department of esophageal surgery at Tokushima University Hospital has been performing NAC with thorough perioperative nutritional management in cooperation with the Nutrition Support Team (NST) since 2012. The team was expanded to include physical therapists, speech therapists, dentists, and dental hygienists, and in 2017 became established as a periOPERAtive assist team (OPERA) with the addition of pharmacists and nurses. In the present study, we retrospectively examined whether perioperative assist team care interventions are effective in reducing adverse events of NAC and improving postoperative outcomes.

PATIENTS AND METHODS

Patients

This study included 109 patients with esophageal cancer who underwent esophagectomy after NAC at Tokushima University Hospital from January 2009 to December 2018. Perioperative management by multidisciplinary team intervention was introduced in 2014. Accordingly, patients were divided into two time periods : from 2009 to 2013, during which no intervention was provided (N group : 52 patients), and from 2014 to 2018, during which the OPERA intervention was provided (O group : 57 patients). We retrospectively investigated whether the OPERA intervention was effective in reducing chemotherapy-related adverse events and improving postoperative outcomes using a prospectively constructed clinical database in our department. This study was approved by the ethics committee of Tokushima

University Hospital.

Perioperative assist team (OPERA)

Fig. 1 shows the history of the establishment of the OPERA. Tokushima University Faculty of Medicine is the only national university system in Japan that has a School of Medicine and a School of Medical Nutrition that work hand in hand to improve QOL of patients. Since 2012, we have been performing not only perioperative chemotherapy but also NAC with thorough nutritional management by NST for patients undergoing esophageal cancer treatment. The perioperative team was joined by a physical therapist in 2013 and a dentist, a dental hygienist, and a speech therapist in 2014. In 2017, the OPERA was formed with the addition of pharmacists and nurses.

OPERA intervention schedule

Fig. 2 shows the OPERA intervention schedule. The OPERA intervention begins at the time of first admission for chemotherapy. Oral care by a dentist as well as NST and physiotherapist intervention is important during chemotherapy. The time from chemotherapy to surgery is approximately one month. Thorough multidisciplinary team intervention is provided continuously from NAC to surgery and finally to discharge. As a team activity, a multidisciplinary joint conference is held every week to consider comprehensive care that matches the condition of each patient. In addition, rounds are conducted by the multidisciplinary team. The same staff members provide intervention from preoperative chemotherapy to surgery and discharge in a consistent manner. The perioperative assist team sets target indicators for nutritional therapy and physical therapy during the perioperative period. Nutritional management uses SGA (Subjective Global Assessment) to evaluate nutrition before treatment, and nutritional management is performed with the goal of achieving SGA : A. In addition, physical therapy is evaluated using the PS (Performance Status Scale), and rehabilitation interventions are performed with the goal of achieving a PS of 0.

Neoadjuvant chemotherapy

All patients underwent primary chemotherapy with docetaxel (DTX), fluorouracil (5-FU), and cisplatin (CDDP). The chemotherapy schedule consisted of the administration of DTX 25 mg/m^2/day on day 1, 5-FU 370 mg/m^2/day on days 1–5, and CDDP 6 mg/m^2/day on days 1–5. This three-agent regimen was repeated every week for 4 weeks as one course (8) unless the patient showed disease progression or experienced an adverse event that could not be controlled.

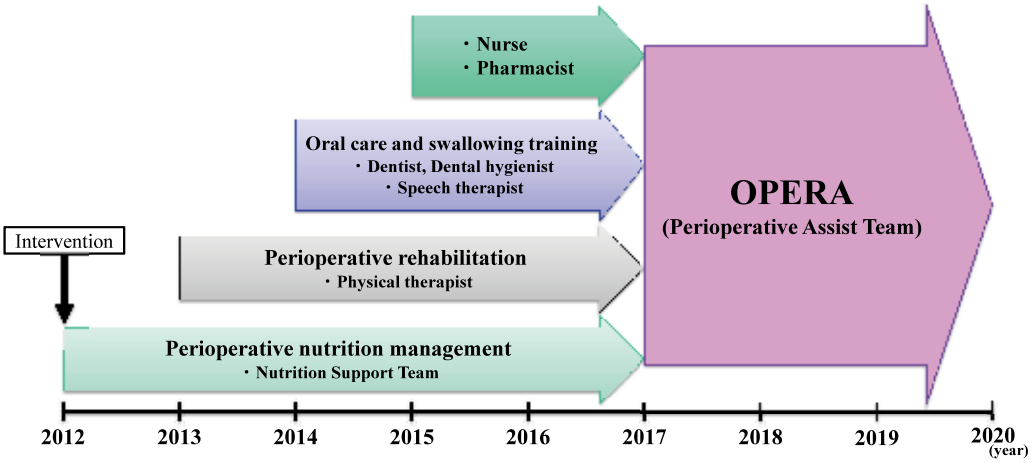


Fig. 1. History of the establishment of the perioperative assist team (OPERA)

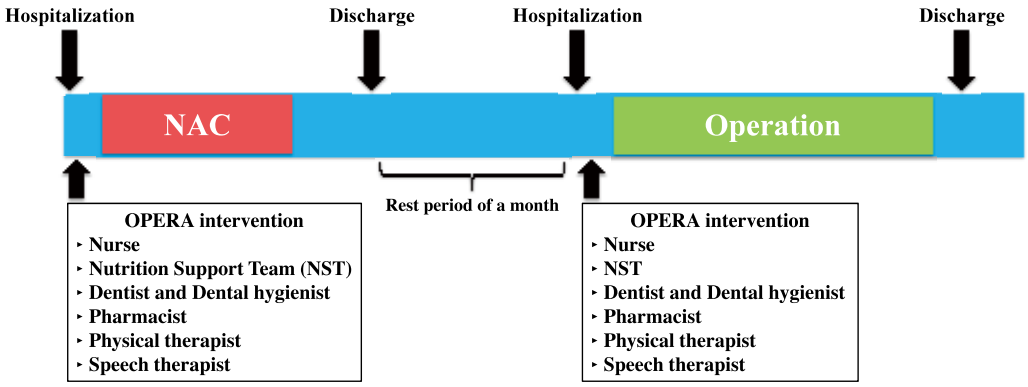


Fig. 2. OPERA intervention schedule for patients receiving neoadjuvant chemotherapy prior to esophagectomy

Surgery

Surgery was performed 4–5 weeks after the neoadjuvant chemotherapy. The cT4 cases responding to the chemotherapy were candidates for surgery. A trans-thoracic esophagectomy and a three-felds lymphadenectomy with reconstruction using the gastric tube conduit through the retrosternal or posterior mediastinal routes were performed. Radical resection was performed in all patients.

Statistical analysis

All statistical analyses were performed using SPSS 22.0 (SPSS, Chicago, IL). Clinicopathologic factors were noted according to the Japanese Esophageal Cancer Classification (9, 10). Adverse events during NAC were evaluated from the first day of NAC until the day of esophagectomy, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE ver. 5.0) (11). In this study, adverse events of chemotherapy were defined as grade 3 or higher according to CTCAE ver. 5.0. Postoperative complications were defined as grade II or higher using the Clavien–Dindo classification (12). Changes in body weight during the perioperative period were also examined by comparing body weight before chemotherapy and after chemotherapy, and between the weight before surgery with that at the time of discharge from the hospital. The rate of body weight decreases was compared by medians at two times points of before chemotherapy and after chemotherapy, and between before surgery and postoperative discharge.

Data are presented as mean±standard deviation (SD), or median and interquartile range (IQR) for variables with a skewed distribution, or number [proportion (%)]. To assess differences between the two groups, the Mann–Whitney test for continuous variables and the χ^2 test or the Fisher's exact test for categorical variables were performed. Differences were considered significant if the P-value was <0.05. Overall survival (OS) was calculated from the date of an individual patient's treatment initiation to the date of last follow-up or the date of death due to any cause. If patients were alive, they were censored at their last follow-up date. OS rates were analyzed using the Kaplan–Meier method and compared using the log-rank test.

RESULTS

Table 1 shows the characteristics of patients in each group. No significant differences were observed in sex, age, PS, SGA, histology, tumor site, preoperative treatment, T factor, N factor, M factor, and disease stage.

Table 2 shows the adverse events of 109 patients who received NAC. The incidence of chemotherapy-related adverse events was significantly reduced in the O group (P=0.002). The proportions of patients with anorexia, diarrhea, and febrile neutropenia were

Table 1. Patient characteristics

	N group (n = 52)	O group (n = 57)	P-Value
Sex (M/F)	43 / 9	47 / 10	0.974
Age (year)	65.3 ± 9.9	65.3 ± 9.2	0.987
PS (0·1 / 2·3)	15·34 / 3·0	42·4 / 1·0	0.275
SGA (A / B·C)	36 / 15·1	44 / 11·2	0.347
Histological type (SCC/other)	47 / 5	53 / 4	0.442
Tumor location (Ce·Ut·Mt / Lt·Ae)	1·4·22 / 19·6	1·6·31 / 18·1	0.117
T factor (1·2 / 3·4)	3·5 / 24·20	4·12 / 35·6	0.110
N factor (0·1 / 2·3·4)	8·12 / 22·7·3	8·21 / 19·6·3	0.193
M factor (0/1)	52 / 0	57 / 0	–
Stage (I·II / III·IVa·IVb)	2·8 / 22·19·1	2·12 / 36·6·1	0.502

PS Performance Status, *SGA* Subjective Global Assessment

Table 2. The incidence of chemotherapy-ralated adverse events

	N group (n = 52)	O group (n = 57)	P-Value
Adverse events of chemotherapy			
Total	30 (57.7%)	16 (28.1%)	0.002
Anorexia	18 (34.6%)	3 (5.3%)	<0.001
Oral mucositis	5 (9.6%)	2 (3.5%)	0.183
Diarrhea	22 (42.3%)	9 (15.8%)	0.002
Leukopenia	6 (11.5%)	4 (7.0%)	0.414
Neutropenia	6 (11.5%)	4 (7.0%)	0.414
Febrile neutropenia	10 (19.2%)	3 (5.3%)	0.025
Dose reduction of chemotherapy	10 (19.2%)	6 (10.5%)	0.200
Discontinuation of chemotherapy	9 (17.3%)	5 (8.8%)	0.183

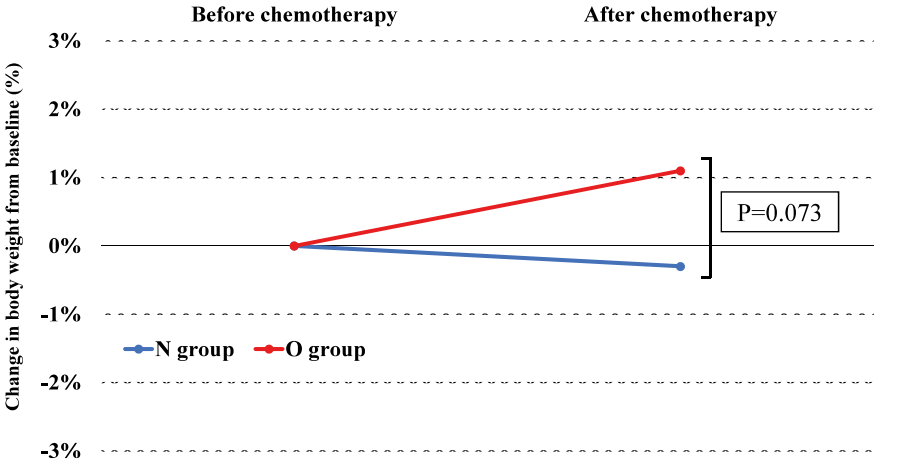
significantly lower in the O group than in the N group (P<0.001, P=0.002, and P=0.025, respectively). There was no difference between the two groups in cases where the dose of chemotherapy was reduced (P=0.200). Although no significant difference was observed, the number of patients who discontinued chemotherapy was lower in the O group than in the N group (P=0.183).

Table 3 shows postoperative outcomes and complications. The average walking start date was 2.0 (IQR : 2.0–2.0) days in the O group, which was significantly earlier than 4.0 (IQR : 3.0–5.7) days in the N group (P<0.001). The average meal start date was significantly later in the O group (P=0.015). There was no difference in the length of hospital stay (P=0.176). Regarding postoperative complications, the number of all complications showed a decreasing trend from 57.7% in group N to 40.4% in group I (P=0.070). The incidence of pneumonia was significantly decreased from 13.5% in group N to 1.8% in group I (P=0.022). There was a non-significant trend toward a decreased incidence of postoperative delirium (P=0.154).

Fig. 3 shows weight loss rate before and after chemotherapy. The rate was -0.3% in group N, but 1.1% in group I. Although the

Table 3. Postoperative outcomes and complications

	N group (n = 52)	O group (n = 57)	P-Value
Outcome after surgery			
Walking start date (day)	4.0 (3.0-5.7)	2.0 (2.0-2.0)	<0.001
Meal start date (day)	9.0 (8.0-10.0)	8.0 (7.0-9.0)	0.015
Length of the hospital stay (day)	25.0 (21-37)	25.0 (17.0-36.5)	0.176
Postoperative complication			
Total	30 (57.7%)	23 (40.4%)	0.070
Anastomotic leakage	7 (13.5%)	3 (5.3%)	0.139
Anastomotic stenosis	5 (9.6%)	5 (8.8%)	0.569
Surgical site infection (SSI)	3 (5.8%)	6 (10.5%)	0.293
Ileus	3 (5.8%)	1 (1.8%)	0.275
Pneumonia	7 (13.5%)	1 (1.8%)	0.022
Chyle chest	1 (1.9%)	2 (3.5%)	0.535
Delirium	4 (7.7%)	1 (1.8%)	0.154
Other	6 (11.5%)	5 (8.8%)	0.632

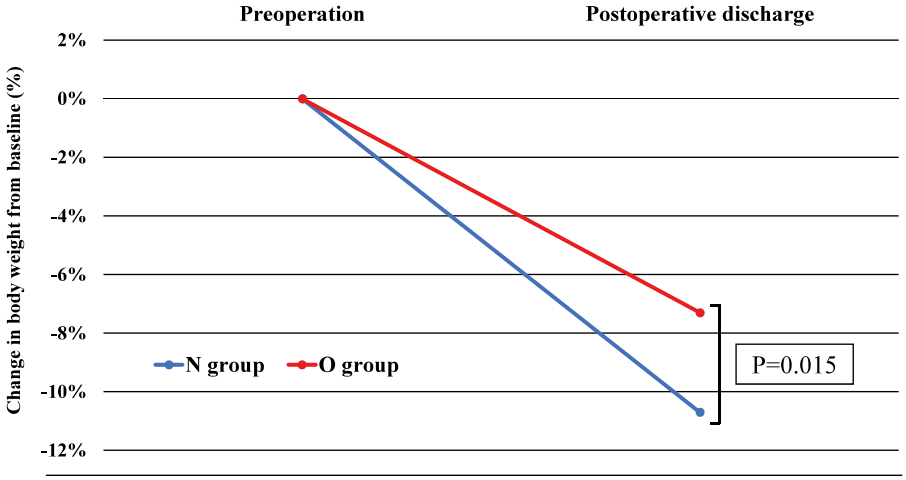


	n		Before chemotherapy	After chemotherapy
N group	52	median (IQR)	0 %	-0.3 (-11.9 — 15.4) %
O group	57	median (IQR)	0 %	1.1 (-14.1 — 15.7) %

Fig. 3. Changes in body weight from baseline (%) in the perioperative period.
The table shows the median and IQR for each group. Statistical comparisons between the N and O groups were performed using nonparametric test. At the time of postoperative discharge, N group was significantly greater weight loss compared to O group (P=0.015).

difference was not clearly significant, the OPERA intervention appeared to prevent weight loss after chemotherapy (P=0.073). Fig. 4 shows weight loss rates during the perioperative period. At the time of postoperative discharge, N group was significantly greater weight loss compared to O group (P=0.015). The weight loss rate was 7.3% in O group, while the weight loss rate was 10.7% in N group. Thus, the OPERA intervention significantly reduced weight loss after surgery for esophagectomy.

We analyzed the relationship between prognosis and OPERA intervention. Median follow-up for censored cases was 5.5 years (range : 0.5–12.2 years) from the date of first-line chemotherapy. The OS curves with the OPERA intervention are shown in Fig. 5. The 5-year survival rate was significantly longer in the O group than in the N group (P=0.003).



	n		Preoperation	Postoperative discharge
N group	52	median (IQR)	0 %	-10.7 (-4.5 — -13.8) %
O group	57	median (IQR)	0 %	-7.3 (-4.5 — -9.6) %

Fig. 4. Prognosis after esophagectomy involving OPERA intervention
Kaplan–Meier curves generated by the log-rank test for overall survival (OS) are shown for the intervention and non-intervention groups.

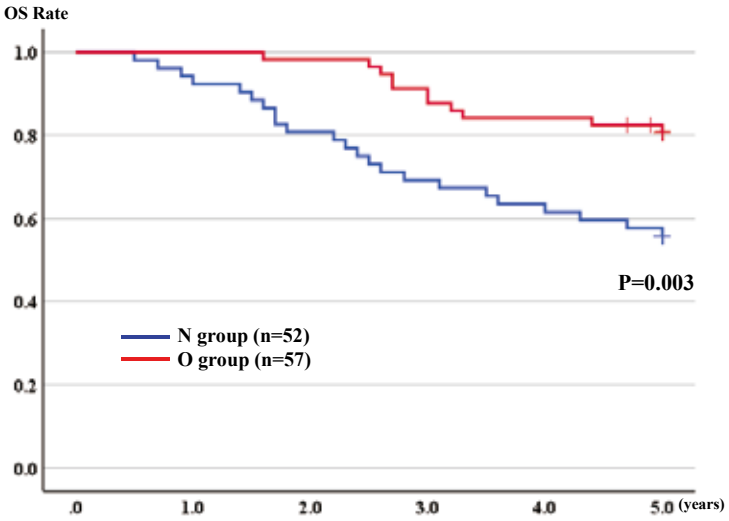


Fig 5.

DISCUSSION

The OPERA intervention reduced the incidence of chemotherapy-related adverse events. Moreover, the number of patients with perioperative weight loss decreased, suggesting that the improved preoperative condition led to reduced postoperative complications. The OPERA intervention was able to accelerate postoperative recovery and postoperative walking was started earlier, and this likely led to a decrease in the occurrence of pneumonia and delirium (13). The OPERA intervention was also shown to be effective for the perioperative management of esophageal cancer. Furthermore, analysis of the relationship between prognosis and OPERA intervention suggested that the OPERA intervention prolonged OS. These findings support the feasibility of safe perioperative management of esophageal cancer patients through multidisciplinary team interventions. In particular, improvements in patient understanding, interest, and cooperation were observed, and further improvements in outcomes can be expected by promoting stronger team medical care in the future. Indeed, we have reported that oral care interventions during the perioperative period in patients with esophageal cancer significantly reduced postoperative pneumonia (14). The OPERA intervention reduced diarrhea and febrile neutropenia, which are adverse events of chemotherapy. NST interventions involve replenishing deficient nutrients through nutritional assessment prior to chemotherapy and improving nutritional intake by changing dietary patterns. Therefore, it is possible that improved dietary habits may have suppressed the onset of diarrhea through adequate nutritional management. In addition, the intervention by a physical therapist was thought to have suppressed diarrhea by improving intestinal motility through moderate daily rehabilitation. The direct reason for the reduction in febrile neutropenia seen during chemotherapy with the OPERA intervention is not clear. However, through intervention, patients were able to maintain good general condition by continuing supportive care such as nutritional management, oral care, and rehabilitation. Although the OPERA intervention did not prevent the decline in white blood cells and neutrophils, it may have prevented the patient from progressing to FN, which is complicated by fever. Based on these findings, OPERA intervention was considered to be an effective method for preoperative chemotherapy.

Our OPERA interventions begin at the time of first admission for NAC and continue through surgery and discharge over a long-term period. Moreover, because the same staff members remain in charge, the patients' trust and sense of security are strengthened, and interventions are provided smoothly and consistently from hospitalization to post-discharge outpatient visits. Multidisciplinary participation has been shown to enable comprehensive care from various perspectives (3, 4, 7). However, the implementation of multidisciplinary team interventions requires a clinical pathway and efficient team medical care. In our department, clinical pathways are used for not only surgery but also NAC. Because clinical pathways allow members of various professions to share information, including the progress of treatment in patients, and are effective for preventing incidents such as inputting errors in order entry (15, 16), they can facilitate multidisciplinary team interventions to reduce adverse events during chemotherapy and postoperative complications.

Perioperative assist team interventions are important for esophageal cancer patients who often have multiple cancers and various medical histories with declining cognitive and physical abilities. Although this study was retrospective in nature, we were able to demonstrate that multidisciplinary team interventions significantly improved outcomes in patients with esophageal cancer. Improving the completion rate of NAC is considered to contribute to improving prognosis. In addition, a reduction in infectious complications has been reported to improve prognosis after esophagectomy (17-19). In the present study, it is likely that the reduced incidence of pneumonia led to improved prognosis. The reduction of postoperative complications, especially postoperative delirium that is common among elderly patients, decreases the burden on medical staff and improves medical safety for patients (20). In the future, by implementing long-term outpatient intervention that is not limited to the perioperative period, malnutrition prevalent in postoperative patients may be prevented.

There are three important elements in perioperative team care. First, a clinical pathway is created to facilitate information-sharing among multidisciplinary medical professionals. It is also important to provide feedback to patients and to increase and maintain the motivation of patients as well as medical staff. Second, an objective evaluation is conducted using nutritional indicators, and appropriate guidance is provided as a team to achieve goals derived from the evaluation. Third, the ability of each staff member needs to be improved, such as by acquiring and maintaining qualifications. In addition, multidisciplinary teams require cohesiveness. Surgeons play a key role in forming and nurturing multidisciplinary teams, and efforts are required to enhance unity by exercising leadership. Whereas regular conferences and rounds are essential, it is also important to exchange information outside the workplace. In Japan, there is no additional medical remuneration for creating or maintaining a team yet. Multidisciplinary team medical care not only improves the QOL and prognosis of patients but also reduces medical expenses by reducing complications, leading to the promotion of work style reforms for medical professionals. Because multidisciplinary team medical care plays a pivotal role in perioperative management, its service should be duly reflected in medical fees.

Multidisciplinary team interventions integrate the expertise of each medical professional to provide the best possible care for patients. Moreover, understanding patient information from various perspectives and providing feedback will enhance the patient's motivation for treatment, which is the most important goal of multidisciplinary team intervention. Furthermore, the smooth functioning of team medical care may reduce the workload of medical personnel including surgeons.

CONCLUSIONS

The OPERA intervention reduced the incidence of chemotherapy-related adverse events and postoperative complications and improved prognosis. Multidisciplinary team interventions integrate the expertise of each medical professional to provide the best possible care for patients. Moreover, understanding patient information from various perspectives and providing feedback will enhance the patient's motivation for treatment.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical statement

All procedures were performed in accordance with the ethical standards of the institutional committee on human experimentation and the Helsinki Declaration of 1964 and later versions. Informed consent or its equivalent was obtained from all patients included in this study.

Conflict of interest

The author declares no potential conflicts of interest associated with this study.

ACKNOWLEDGMENTS

The author gratefully acknowledges Emeritus Professor Akira Tangoku of the Department of Thoracic, Endocrine Surgery and Oncology, Tokushima University Graduate School of Biomedical Sciences, for supervising this study.

Funding : No funding was received for this study.

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