

# Assessment of results of thoraco - laparoscopic esophagectomy in patients receiving neoadjuvant chemoradiotherapy for esophageal cancers

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## Abstract

*Introduction:* Laparoscopic esophagectomy plays an important role in esophageal cancer. In recent years, the treatment of esophageal cancer is multidisciplinary, especially in neoadjuvant chemoradiotherapy for stages from IIB-IV to downstage to increase the possibility of R0 resection and survival. Globally, there have many studies showing the feasibility, safety, and effectiveness of laparoscopic esophagectomy after neoadjuvant chemoradiotherapy in patients with esophageal cancers. In Vietnam, there has been a paucity of data and surgical results in this group of patients. Therefore, we conducted a study to evaluate the safety, feasibility, and effectiveness of laparoscopic esophagectomy in patients receiving neoadjuvant chemoradiotherapy for esophageal cancers at Viet Duc Hospital.

*Patients and methods:* A retrospective study of patients who underwent the thoraco-laparoscopic esophagectomy receiving neoadjuvant chemoradiotherapy at Viet Duc hospital from T9/ 2021- T9/2021.

*Results:* From September 2017 to September 2021, there were 30 patients with esophageal cancer receiving neoadjuvant chemoradiotherapy followed by thoraco-laparoscopic esophagectomy. 100% were male, the mean age was 55.2 years old. Tumor locations in the middle and lower third parts were 53.3% and 46.7% respectively. 96.7% was squamous cell carcinoma, adenocarcinoma accounted for 3.3%. Before chemoradiotherapy stage III, and IV was 80%; 16.7%, after chemoradiotherapy, stages II and III were 43.3% and 40%. The average operation duration was 283 minutes, the average blood loss during video assisted thoracotomy was 60ml, there were no intraoperative complications, and there were no cases requiring conversion to open thoracotomy. The duration of intubation was 2.1 days, the average hospital stay was 12.5 days. There were 13.3% respiratory complications and 6.7% had experienced anastomosis leak. There were no postoperative deaths. The average number of harvested lymph nodes was 19, the lymph node metastasis rate was 43%. R0 resection rate was 93,4%. The results were 40% consistent completely with the histopathological examination. The mean survival time after surgery was  $27 \pm 3.7$  (months), and the survival rate after 2 years was 42%.

**Conclusions:** Thoraco-laparoscopic esophagectomy after neoadjuvant chemoradiotherapy is a feasible, safe, and beneficial procedure for post-surgery recovery of patients.

**Keywords:** Esophageal cancer, Thoraco-laparoscopic esophagectomy, neoadjuvant chemoradiotherapy.

## Introduction

Esophageal cancer is the 9<sup>th</sup> most common cancer and the 6<sup>th</sup> common cause of cancer death worldwide, while in Viet Nam, esophageal cancer is ranked 14<sup>th</sup> in which each year has more than 30000 new cases [1]. In previous decades, surgery remains a crucial treatment for esophageal cancer, giving good results for early stages (T1-T2), however in advanced stages (T3-T4), the long-term outcome is still low. This has motivated researchers to explore multimodality treatment solutions that are more effective, especially neoadjuvant (neoadjuvant chemoradiotherapy) for IIB-IV stages to achieve better results. Response evaluation standard criteria after chemoradiotherapy are divided into 3 levels (according to RECIST - Response Evaluation Criteria in Solid Tumours): complete response, partial response, and no response (the disease stays the same or develops). It depends on the type of concurrent chemoradiotherapy regimen to have different response rates. According to Kato K report [2] that combines CF regimen and radiation of a total 60Gy dose, the complete response result was 62,2%. According to Simon [3], the rate of complete response was 55,6%, partial response was 27,7% and no response was 16,7%. The clinical trial studies by Tepper J [4], Cao XF [5] concurrently showed esophagectomy after neoadjuvant chemoradiotherapy for advanced esophageal cancer produced better outcomes than surgery alone. CROSS research by Hagen et al [6] also showed similar benefits: increased R0 resection rate, reduced lymph node metastasis rate, and prolonged survival rate, whilst not increasing postoperative mortality.

However, many studies exhibited the disadvantages of neoadjuvant chemotherapy. Adverse effects including esophagitis, dermatitis, weight loss, nausea, leukopenia, anemia, thrombocytopenia occurred [6]. Other studies by Mariette [7], Kumagai K [8] also showed several post-operative complications typically related to respiratory, anastomotic leaks, mortality rate was more common in a group of patients receiving neoadjuvant chemoradiotherapy. The safety and feasibility of laparoscopic esophagectomy have been well accredited and the long-term survival rate is similar to open surgery, laparoscopic surgery even has more advantages than conventional surgery: reduce complications, early recovery, and improved life quality after surgery [9]. In Viet Nam, thoraco-laparoscopic esophagectomy to treat esophageal cancer had been performed by many authors at major centers in the 2010s like Pham Duc Huan, Trieu Trieu Duong, Lam Viet Trung... In Viet Nam, although neoadjuvant chemotherapy has also been implemented for patients with esophageal cancer in the advanced stage, yet there haven't had many data of results in this group of patients. Hence, we conduct this study to evaluate the result of thoraco-laparoscopic esophagectomy in esophageal cancer patients who had neoadjuvant chemotherapy at Viet Duc University Hospital.

## Patients and methods

Esophageal cancer patients staging IIB-IV with neoadjuvant chemoradiotherapy, and thoraco-laparoscopic esophagectomy at Viet Duc University Hospital from September 2017 to September 2021 were enrolled.

**Selection criteria:**

Patients were diagnosed with esophageal cancer located at 1/3 middle and lower according to endoscopy and biopsy results.

Esophageal cancer staging IIb-IV was evaluated through CT scan and endoscopic ultrasound before neoadjuvant chemotherapy.

Patients receiving neoadjuvant chemotherapy were re-examined after that treatment through CT scan, endoscopic ultrasound.

Patients underwent thoraco-laparoscopic esophagectomy at Viet Duc University Hospital from September 2017 to September 2021.

**Exclusion criteria:**

Patient with esophageal cancer located at 1/3 upper part.

Patients with esophageal cancer received chemoradiotherapy but did not have operations.

**Study methodology:** description retrospective, cross-sectional study

**Study procedure:** Selecting medical reports met with selection criteria. Collecting data according to designed medical report for study. Surgical outcome assessment was conducted by follow-up and gather patient relatives information (patient was invited for a check after follow-up or obtained particular information from family in case the patient had already died).

**Video Assisted Thoracotomy (VAT) phase:**

Patient was in prone position, rotated to the left 30 degrees. During thoracotomy phase, patients right lung was deflated with a double-lumen endotracheal tube. We often use 4 trocars.

Esophageal dissection technique: initially, we probed the tumor resection possibility which if detected removable, we would start with dissection, ligation, clipping, and resecting the azygos vein and then the right bronchial artery for esophageal dissection. Removing right lung triangle ligament, open mediastinal pleura, proceed to esophageal dissection and wall lymph node resection into "enblock".

**Laparoscopic surgery phase:**

- We placed 5 trocars.
- Released greater curvature of stomach, carefully

preserved the integrity of gastroepiploic arterial arcade along the greater curvature and the right gastroepiploic vessel: removed gastrocolic ligament to insert into omental bursa. On the right side, right gastrocolic ligament was opened to the base of right gastroepiploic vessel, completely released greater curvature of stomach.

- Opened gastrohepatic ligament to right crus of diaphragm: from liver pedicle releasing stomach lesser curvature (lymphadenectomy group 1). Continued to perform lymphadenectomy group 8a, 12a, removed left gastroepiploic artery, lymphadenectomy group 7,9,11p. Continued to open peritoneal cavity to the left that had already been dissected, lymphadenectomy group 1. Completely separated abdominal esophagus from the diaphragm hiatus, widened diaphragm hiatus.

**Cervical phase:**

Cervical incision in J-sharp at the anterior border of left sternocleidomastoid muscle.

Pulled up the esophagus to dissect posterior site upwards and down to the chest. Cut the cervical esophagus in half at the level of thyroid gland's lower border, closed the lower end of the esophagus, and pulled down the entire esophagus to the abdomen.

Gastric tube reconstruction: large tube or whole stomach.

Pulled up the gastric tube through the posterior mediastinum to the neck for termino-terminal anastomosis or termino-lateral anastomosis with Maxon 3-0.

Research variables: characteristics of patient, neoadjuvant chemoradiotherapy and after surgery data (based on endoscopic result, endoscopic ultrasound, thoracic CT scan with contrast...), surgical technique, post-surgery complications, length of stay in ICU, postoperative hospitalization stay, amount of lymph nodes harvested, lymph node metastasis rate, degree of RO, histopathological response rate, survival time after surgery.

**Data processing:** Statistical analysis using SPSS 16.0 software. Survival time post-surgery was calculated using Kaplan Meier method.

**Results**

In 4 years, from September 2017 to September 2021 there were 30 patients with esophageal cancer receiving neoadjuvant chemotherapy underwent thoraco- laparoscopic esophagectomy at Viet Duc University Hospital.

Table 1: Patient characteristics

| Patient characteristics       |                                | (n = 30)   |
|-------------------------------|--------------------------------|------------|
| Average age                   | 55,2 ± 1,7 (42 - 68) years old |            |
| Gender                        | Male                           | 30 (100%)  |
|                               | Female                         | 0 (0%)     |
| Tumor location                | 1/3 middle                     | 16 (53,3%) |
|                               | 1/3 lower                      | 14 (46,7%) |
| Histopathological type        | Squamous Carcinoma             | 29 (96,7%) |
|                               | Adenocarcinoma                 | 1 (3,3%)   |
| Neoadjuvant chemoradiotherapy | Stage 1                        | 0 (0%)     |
|                               | Stage 2                        | 1 (3,3%)   |
|                               | Stage 3                        | 24 (80%)   |
|                               | Stage 4                        | 5 (16,7%)  |
| Post-chemoradiotherapy        | Stage 1                        | 4 (13,4%)  |
|                               | Stage 2                        | 13 (43,3%) |
|                               | Stage 3                        | 12 (40%)   |
|                               | Stage 4                        | 1 (3,3%)   |
| Chemoradiotherapy response    | Complete response              | 14 (46,7%) |
|                               | Partial response               | 15 (50%)   |
|                               | No response                    | 1 (3,3%)   |

Period for performing surgery after finished chemoradiotherapy: 5,1 ± 1,8 weeks (3-12 weeks)

Table 2: Results of surgical treatment

| Patient characteristics  |                                | (n=30) |
|--|--------------------------------|--------|
| Time of surgery  | 283± 43,6 mins (180- 360 mins) |        |
| Converted to surgery (thoracic phase)  | 0 (0%)                         |        |
| Complications during operation (esophagus injury, artery injury, thoracic tube injury ...) | 0 (0%)                         |        |
| Amount of intraoperative blood loss (thoracic phase)                                       | 60±11,1 (ml) (50-100 ml)       |        |
| Number of days in ICU  | 2,07±1,23 (1-6 day)            |        |
| Number of days hospitalized  | 12,47± 5,2 (9-38 days)         |        |

|               |  |           |
|---------------|--|-----------|
| Complications | Respiratory complications                                    | 4 (13,3%) |
|               | Cardiac complications (arrhythmia, myocardial infarction...) | 0 (0%)    |
|               | Deep vein thrombosis   | 0 (0%)    |
|               | Anastomotic leak   | 2 (6,7%)  |
|               | Chyle leak   | 0 (0%)    |
|               | Bleeding after surgery                                       | 0 (0%)    |
|               | Dead   | 0 (0%)    |

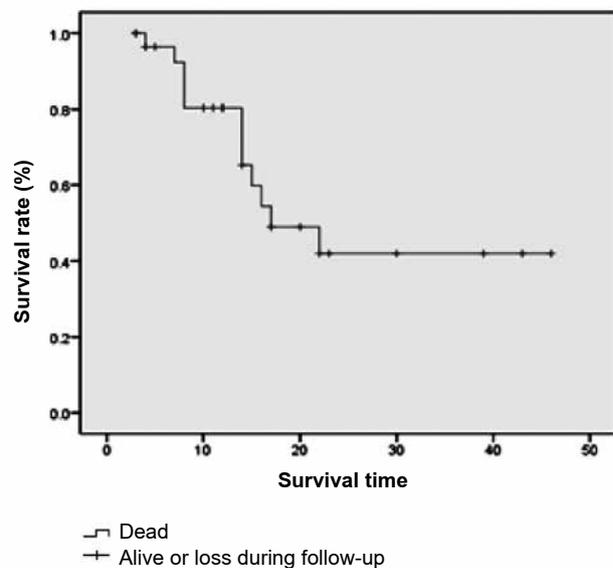
Table 3: Oncological result after surgery

| Patient characteristics             |    | (n=30) | (%)  |
|-------------------------------------|----|--------|------|
| Average amount of lymphadenectomy   |    |        |      |
| Radical resection rate              | R0 | 28     | 93,4 |
|                                     | R1 | 1      | 3,3  |
|                                     | R2 | 1      | 3,3  |
| Complete histopathological response |    | 12     | 40%  |

**The rate of lymph node metastasis in our research is 43%**

**Comments:** Average amount of lymphadenectomy was 19 lymph nodes. Radical resection rate of R0, R1, R2 were 93,4%; 3,3% and 3,3% respectively. Complete histopathological response was 40%.

Table 4: Postoperative survival rates



**Comments:** Average survival rate was  $27\pm 3,7$  (months); the rate of surviving 2 more years in study in 42%.

## Discussions

Esophageal cancer is common among men and in the elderly group from 60-70 years old [11]. In our research, 100% patients were male, and the mean age was 55 years old (Table 1). This result was similar to Pham Duc Huan [12] and Trieu Truong Duong [13]. This could be a result of smoking and drinking alcohol habit which is pretty high in Viet Nam, especially males. Histopathologically, 96,7% was Squamous cell carcinoma, only one patient (3,3%) has adenocarcinoma. (Table 1). This result was consistent with Pham Duc Huan [12], Baofu Chne [14] esophageal squamous cell carcinoma accounted for 93.5% and 92.3%, respectively. However, when compared to international authors, especially European and American countries, adenocarcinoma type in esophageal cancer is quite high (64-68,3%), and often occurs in the gastroesophageal junction [15]. The reason for this difference may be because of smoking a lot of cigarettes, and drinking alcohol in Viet Nam and Asian countries, while in European and American countries, may be related to Barrett esophageal diseases, gastro-oesophageal reflux disease, obesity and HP infection [16]

In our series, before chemoradiotherapy, the number of patients at stages III, IV mostly accounted for 80% and 16,7% respectively. However, after chemoradiotherapy, stages II and III mostly accounted for 43,3% and 40% respectively (Table 2). Therefore, neojuvant chemoradiotherapy has the effect of attenuating severity, increasing the probability of surgical treatment. A report by Nguyen Duc Loi [17], showed that after chemoradiotherapy there was 31,1% of patients responded fully, 53,8% partly responded, 12,9% of patients with no response, and 2,2% had the disease developed (according to RECIST standard). Joachim W Heise et al [18] showed chemoradiotherapy before surgery would

reduce tumor size in 23 out of 33 cases (70%), no change was found in 7 patients (21%), and improved in 3 patients (9%), and there was no difference in response rate between chemoradiotherapy or simply neoadjuvant chemotherapy. Depending on each center that can choose chemoradiotherapy, or simple neoadjuvant chemotherapy, select different regimens ... will have different response rates, but basically both reduce tumor size, down stage and increase the ability of R0 resection.

There are concerns that neoadjuvant chemoradiotherapy might complicate laparoscopic surgery, and increase the risk of complications [19]. In addition, esophageal cancer in the advanced stage is often located near the aorta, trachea and damage to any structure can cause significant complications. In our research, the average time for surgery is  $283\pm 43,6$  mins, the amount of intraoperative blood loss (during thoracotomy) about 60ml, and we did not come across complications during the surgery: such as tracheobronchial damage, aortic injury, chyle duct injury, as well as not had to convert to open surgery during thoracotomy. Research by Guangyuan Liu [20], the average surgical time in the group with neoadjuvant chemoradiotherapy was 253 mins, 5/44 patients in the group receiving neoadjuvant chemoradiotherapy had to be converted open surgery during thoracotomy, the main causes are adhesions of the pleural cavity, many fibrous lesions that are difficult to manipulate and require ventilation of 2 lungs to ensure stable breathing. The clinical trial study of Mohammadtaghi [21] found that the surgical time and intraoperative blood loss in neoadjuvant chemoradiotherapy group were significantly higher than in the group treated by surgery alone ( $p<0,05$ ). This can be explained as neoadjuvant chemoradiotherapy can cause local tissue edema, fibrosis, and difficulty identifying anatomical structures and layers. From our experience, we should assess the ability of tumor mobilization related to tracheobronchial and

aorta sites, before deciding on esophagectomy. When deciding to remove the esophagus, we should start from the healthy areas and gradually expand to lesion areas. And today, combined with advances in chemo/radiation technology, it is possible to significantly reduce damage to normal tissues and associated complications.

The average time after completing neoadjuvant chemoradiotherapy for surgery in our study was 5,1 weeks. In Simon Rohs research [22] it was 4 weeks. In the report, the authors also showed the group that had surgery <35 days after completing the neoadjuvant chemoradiotherapy had anastomotic leak rate lower compared to the group that had surgery >35 days (after finished chemoradiotherapy). Research by Shaikh et al [23], Anna Lee [24] showed that extending the surgical period after neoadjuvant chemoradiotherapy may increase the histopathologic complete response rate, however, did not prolong survival after surgery. Most studies recommended esophagectomy from 3-8 weeks after having completed neoadjuvant chemoradiotherapy [11], [22], [24].

The length of stay in ICU in our study was 2 days and the average hospitalization after surgery was 12,5 days; our result was similar to other authors in the world such as research by Reza Bagheria [25] with the length of stay in ICU, and hospitalization was 1,9 day and 11,6 days respectively. Research by Guangyuan Liu [20], Mohammadtaghi R. M [21] the hospitalization after surgery in chemoradiotherapy group was 12,8 days and 12 days. Our study did not compare with the group that had surgery alone, but when reviewing the studies of other authors, Reza Bagheria [25] Guangyuan Liu [20], Mohammadtaghi R. M [21], the authors showed that there was no difference in the length of ICU stay and hospital stay between the immediate surgery group and the group receiving neoadjuvant chemoradiotherapy ( $p < 0.05$ ). Postoperative complications were a

matter of concern to evaluate the effectiveness of surgery. Many authors believe that neoadjuvant chemoradiotherapy leads to an increased rate of complications after surgery, especially respiratory complications, and anastomotic leak [9], [26]. In our study, 13,3% of patients experienced diverse respiratory complications (pneumonia, pleural effusion, respiratory distress...), anastomotic leak was 6,7%, there were no patients had chylous fistula, or death after surgery. In a study by Hang Tan [27] in the neoadjuvant chemoradiotherapy group, respiratory complications occurred in 9/76 patients (accounted for 11,8%), chylous fistula was encountered in 1/76 patients (1,3%). Simon Rohs study [22] anastomotic leak rate in the neoadjuvant chemoradiotherapy group was 10.3% (24/232 patients), while in Joachim W Heises study [18], the mortality rate in the group of patients receiving neoadjuvant chemoradiotherapy was 6%. Many clinical trials by Van Hagen [6]; Berger [28] showed that postoperative complications such as anastomotic leak, bleeding, respiratory complications, or mortality did not differ between 2 groups of neoadjuvant chemoradiotherapy and group of surgery alone. Research by Ruol et al [26] between 2 groups of patients > 70 years old and group of patients <70 years old, both underwent esophagectomy after neoadjuvant chemoradiotherapy, and the mortality and complications after surgery were not different between 2 groups. However, there are also a few studies that showed neoadjuvant chemoradiotherapy tends to increase cardiovascular and respiratory complications, mainly pneumonia and arrhythmia [20], [29].

Regarding the evaluation of surgical treatment results after neoadjuvant chemoradiotherapy in our study, 93.4% of patients achieved R0, only one patient (3.3%) was R1, and one patient (3.3%) was R2. The case of R1 patient was histopathological examination confirmed the removed circumscision

closed to the tumor, and one R2 patient was at stage IV before surgery because during the operation found that the tumor has invaded the right diaphragmatic column and right pleura so we were unable to perform R0 resection. To evaluate the possibility of surgery after chemoradiotherapy, we relied mainly on thoracic CT scan, gastroscopy to compare 2 periods before and after neoadjuvant chemoradiotherapy, and in some cases which required PET-CT for surgical indications. Our results, similar to Guangyuan Lius study [20], Hang Tan [27], the rate of successfully achieving R0 after neoadjuvant chemoradiotherapy was 95,45%; 93,4%, respectively. The average number of harvested lymph nodes in our study was 19 nodes, with the rate of lymph node metastasis being 43%. This result was similar to Guangyuan Liu result [20], the average number of dredged lymph nodes was 18. The rate of lymph node metastasis in Hang Tan's study [27] was 25%, Van Hagen [6] was 31%, our study was higher than other authors, possibly because patients in our study received chemoradiotherapy at different centers, in which not able to agree on a standard chemoradiotherapy procedure, so the rate of lymph node metastasis was still high. The complete histopathological response in our study was 40%. Research by Simon Roh [22], this rate was 25.9% (60/232 patients), author Guangyuan Liu [20] was 29.55%. This percentage varied in many studies from 20-40% [23]. There were many related factors affecting this difference, including the type of chemoradiotherapy, the dose, the quality of radiation therapy, qualified pathologist... However, according to Van Hagen [6] histopathological response is not a prognostic factor for survival. During the follow-up, we lost information of two patients, 12 patients died. The mean overall survival time of our series was  $27 \pm 3.7$  (months); the 2-year survival rate in this study was 42%. According to Van Hagen's study [6] survival time after surgery in the neoadjuvant chemoradiotherapy group was 49,4

months, and extra survival rate after 2 years was 67%, while in Y. Hamai's study [30], the average survival time was 50 months, survival rate after 2 years was 60%. Compared with other authors' studies in the world, our survival time after surgery was lower, this might be because patients in our study were mainly in stages III, IV (more than 95%); and post-operative lymph node metastasis rate was still high (40%); We have yet applied the standard chemoradiotherapy procedure to all patients in this study, observation time was not long enough. In Van Hagens study [6] Y. Hamai [30] all showed that survival time after surgery and survival rate after 2 years were significantly improved in neoadjuvant chemoradiotherapy group compared with group that had surgery alone ( $p < 0.05$ ).

## Conclusions

Thoraco-laparoscopic esophagectomy after neoadjuvant chemoradiotherapy is feasible, safe, less postoperative complications, and benefits to patients recovery after surgery. The long-term result of survival and extra survival rate in our research require more time to evaluate the effectiveness.

**Conflict of interest:** The authors declare that they have no conflict of interest.

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