Impact of thoracic esophageal displacement after lobectomy on the continuity of oral adjuvant chemotherapy.

Abstract

Background: Adjuvant tegafur-uracil therapy has prolonged postoperative survival in patients with non-small cell lung cancer. Some patients experience treatment discontinuation due to gastrointestinal disorders such as anorexia, and the associated factors and the impact of lobectomy remain unclear. This study aimed to assess the postoperative esophageal displacement after lobectomy and to clarify its impact on the continuity of tegafur-uracil treatment.

Methods: Patients who received adjuvant tegafur-uracil therapy after lobectomy between April 2009 and March 2019 were retrospectively analyzed. Patient background, perioperative characteristics, treatment findings, and the degree of esophageal displacement (DEP) measured by CT were compared between the treatment completion group and the discontinuation group. A subgroup comparative analysis was further performed in the groups divided according to DEP.

Results: A total of 68 patients were reviewed, including 41 males and 27 females with mean age of 66.2 years old. 41 patients completed the 2-year adjuvant treatment and 27 patients discontinued it. The OS and RFS between the two groups were statistically significant (p=0.027, p=0.010). DEP at Th7 level was a significant predictor of treatment discontinuation (p=0.046, odds ratio [OR]: 1.138, 95% confidence interval [CI]: 1.002–1.291). Among the patients with high DEP above the baseline determined from receiver operating characteristic curve, the cause of discontinuation was anorexia, which was significant in multivariate analysis (p = 0.013, OR: 14.72, 95% CI: 1.745–124.2).

Conclusions: Our study suggested that anatomical displacement of the esophagus after lobectomy may affect the discontinuation of oral adjuvant chemotherapy in patients with lung cancer.

Keywords

lung cancer; tegafur-uracil; adjuvant chemotherapy; surgical mortality; mediastinal shift: esophageal displacement

Background

Primary lung cancer is one of the most common causes of cancer-related deaths worldwide and is also the leading cause of cancer-related deaths. For patients with non-small cell lung cancer (NSCLC), surgical treatment is selected according to the cancer stage. However, the 5-year survival rate after complete resection is 60% at all stages, and many patients develop tumor recurrence, so patients in advanced stages require adjuvant chemotherapy [1]. Platinum-based chemotherapy has been reported to improve survival in standard patient regimens for resected stage II or IIIA patients [2, 3]. On the other hand, for patients with completely resected early-stage lung cancer, postoperative adjuvant treatment with oral tegafur-uracil is common, based on the results of a phase III study conducted in 2004 [4]. The 5-year survival rate in the postoperative adjuvant therapy group was 87.9% overall in stage I, while the 5-year survival rate in the surgery-only group was 84.9%, showing a significant difference. This adjuvant treatment has been reported to affect the 5-year survival rate of patients by an additional 14% and reduces the risk of cancer death by 52%. However, with long-term administration over 2 years, only 59%–61% of patients can complete the treatment owing to adverse events [4, 5]. Some of the causes that discontinue treatment are vague, and if they can be reconsidered and predicted from a new perspective, it may lead to improve their survival rate.

Loss of appetite and nausea account for 8.9% of the reasons for discontinuation and are also the main reason for dose reductions [5]. Compared to patients with gastrointestinal cancer, patients with lung cancer experience these symptoms less often after surgery and are less discussed. Predicting if lung cancer patients are more likely to develop this disadvantageous side effect is thought to lead to further improvements in their survival rates by continuing oral administration of tegafur-uracil. We suspected that the anatomical changes in the thoracic cavity, especially thoracic esophagus due to lung resection may have affected the decline in tolerability of tegafur-uracil treatment. Thus, we conducted a retrospective study in patients who underwent oral adjuvant chemotherapy with a complete NSCLC resection.

Material and Methods

Patients

This retrospective study was approved by the institutional review boards at the Shiga University of Medical Science Hospital and waived the requirement for informed consent (approval number R2020-163). We reviewed the medical records of NSCLC patients who received adjuvant chemotherapy with oral tegafur-uracil at the Department of Cardiothoracic

Surgery, Shiga Medical University of Medical Science (Shiga, Japan) between April 2009 and March 2019. Patient characteristics, computed tomography (CT) manifestations, surgical findings, perioperative findings, and treatment outcome were described. Pathological stage was re-evaluated according to the Union for International Cancer Control (UICC) version 7 classification. The observed toxicities during the adjuvant chemotherapy were graded according to Common Toxicity Criteria for Adverse Events Version 4.0 (CTCAE v4.0). Anorexia was defined as loss of appetite resulting from episodes of unpleasant gastrointestinal symptoms except diarrhea and constipation. Postoperative follow-up was performed with imaging examinations performed every 3 to 6 months for at least 5 years after surgery.

We also retrospectively recorded the following variables: sex, age, body mass index; smoking history (Brinkman index); tumor diameter as measured by computed tomography; respiratory function [vital capacity (VC), forced expiratory volume in 1 s ($FEV_{1.0}$), and their predicted values (%VC, % $FEV_{1.0}$)]; surgical findings (procedure, approach), pathological lung tumor findings, oral tegafur-uracil details, and patient outcomes.

Evaluation of esophageal position on chest computed tomography

To investigate the impact of anatomical esophageal displacement, CT images taken before and one year after operation were compared. Image analysis was performed using the measurement function of the integrated image information system Shad-eQuest (Yokogawa Medical Solutions Corporation, Tokyo, Japan). CT images for comparison were aligned at the same cross section in the axial view. Then, we measured the distance from the reference line set as the median, mediastinum to the thoracic esophagus. The measurement was performed at the middle thoracic and lower thoracic esophagus. The middle thoracic esophagus was evaluated at Th7 level, with the line connecting the tracheal bifurcation and the vertebral body as the reference line. The lower thoracic esophagus was evaluated at Th10 level, with the line connecting the left edge of the inferior vena cava (IVC) and the vertebral body as the reference line (Fig. 1). When the position of the esophagus after surgery was located on the left side of the mediastinum, the moving distance was calculated by the following formula: the longer distance, either before or after surgery, minus the other distance (Fig. 1A, 1C, 1D). When the position of the esophagus after surgery was found on the right side of the mediastinum, the moving distance was calculated by the following formula: preoperative distance plus postoperative distance (Fig. 1B). The measurements were performed by the corresponding author and another co-author that was blinded to the patient information.

Statistical analysis

All data were analyzed using SPSS software version 25.0 (IBM, Inc., CA, USA).

Continuous variables were expressed as means ± standard deviations (SD). Survival curves were estimated by the Kaplan-Meier method, and the difference was assessed by means of the log-rank test. The chi-square test and *t*-test were used for comparing categorical and continuous variables respectively. Ordinal variables such as pathological staging and the initial treatment doses of tegafur-uracil were analyzed using the Mann-Whitney *U* test. A receiver operating characteristic (ROC) curve analysis was performed to test a cutoff value of the identified DEP for tegafur-uracil discontinuation. P-values < 0.05 were considered statistically significant.

Results

Fig. 2 summarizes the patients who were analyzed in this study or patients included in this study (n=68). The clinical characteristics of all patients are presented in Table 1. The mean age was 66.2±8.6 years. All patients had N0 primary lung cancer, and lobectomy and lymph node dissections were performed as radical surgery. None had previously undergone surgical resection related to gastric and esophageal disease. Tumor pathological type seen in the highest proportion was adenocarcinoma; in terms of squamous, pleomorphic, and large cell carcinoma, the distribution seen was 10%, 1.4%, and 2.9%, respectively. Drugs were provided as granules in 30 cases and as capsules in 38 cases. Totally 10 patients experienced dose reduction due to increased levels of serum transferase or blood bilirubin (n=6), anorexia (n=1), rash (n=1), stomatitis (n=1) and dizziness (n=1). Adverse events requiring discontinuation of treatment developed in 27 patients, the reasons for which included anorexia (n=10), tumor recurrence (n=6), increased levels of serum transferase or blood bilirubin (n=5), pneumonia (n=3), and others (n=3). All patients with anorexia were classified as CTCAE grade 2 or higher, and their symptoms improved after treatment discontinuation. There were no fatal adverse events. The range of DEP at Th7 level was 0 to 34.3mm and at Th10 level was 0 to 28.6mm, respectively. CT images taken one year after surgery were used for these measurements, except for 3 cases (2 cases of pneumonia and 1 case of tumor recurrence). No findings of esophageal hernia or achalasia were confirmed.

The mean postoperative follow-up duration of all patients was 55 months. During the observation, tumor recurrence was observed in 12 patients, and death as an outcome was observed in 9 patients. Only 2 patients died due to lung cancer. The overall survival (OS) curves and relapse free survival (RFS) curves are shown in Fig. 3A and 3B. The 5-year OS and RFS rates for all patients were 84.8% and 74.3%, respectively. Fig. 3C and 3D shows that the OS rates for the completion and discontinuation groups were 93.2% and 70.7%, respectively (p=0.027). The RFS rates for the completion and discontinuation groups were 77.0% and 58.9%, respectively (p=0.010).

In Table 2, the baseline characteristics and clinicopathological variables of patients in the treatment completion group and the discontinuation group are shown. The multivariate analysis revealed that the postoperative esophageal displacement at Th7 level was an only significant variable related to treatment discontinuation (p=0.046, odds ratio [OR]: 1.138, 95% confidence interval [CI]: 1.002–1.291). ROC curve analysis was performed to determine the accuracy of DEP at Th7 level in treatment discontinuation prediction. Optimal cutoff value was 2.94 mm, exhibiting the sensitivity and specificity of 63.0% and 65.9%, respectively.

Table 3 shows the clinicopathological characteristics classified by this cutoff value. These groups had similar variables and were not statistically significant. The results of logistic analysis with treatment outcome are shown in Table 4. In the 3.0 mm＞DEP group, anorexia was a significant cause of treatment discontinuation (p = 0.013, OR: 14.72, 95% CI: 1.745–124.2).

Discussion

Tegafur-uracil is widely used as an adjuvant chemotherapy for NSCLC, and they have been reported to improve 5-year OS [4,6]. In our study, patients with sufficient treatment showed better prognosis than patients who discontinued treatment, that was equivalent to previous reports. Tegafur-uracil is associated with fewer serious adverse events than cisplatin-based adjuvant chemotherapy [3,4]; it can be administered to the elderly and be used as an outpatient treatment. On the other hand, not a small proportion of adverse events with predominant gastrointestinal symptoms were reported to have led the treatment to fail in 23% of cases, including cancer recurrence [4]. Similarly, in our study, 16 patients (23%) discontinued due to anorexia and tumor recurrence.

There were two reasons for choosing Th7 and Th10 levels in order to perform the image evaluations of the middle and lower thoracic esophageal displacement. First, the upper thoracic esophagus is adjacent to the trachea and aortic arch [7] and is not expected to be displaced, so it was omitted from verification. Second, the tracheal bifurcation and IVC are fixed in the mediastinum and served as a stable marker in determining the median reference line. Anatomical changes that occur after lobectomy vary according to the excision site and individual. Therefore, the setting of this reference line using the constituent organs of the mediastinum as the markers made it possible to stably evaluate the distance to the esophagus (Fig. 1B, 1D). Although the mediastinum was shift after lobectomy, setting a red reference line facilitated the measurement of the yellow line. These procedures were useful in quantifying anatomical esophageal shift after lobectomy, and revealed that displacement of the middle thoracic esophagus affected treatment discontinuation (Table 2, p=0.046). To clarify our hypothesis that esophageal displacement is a factor in anorexia during treatment,

we performed a subgroup analysis focusing on causes for discontinuation. Here, the cut-off value of DEP at Th7 level was determined by ROC analysis and classified into high DEP group and mild DEP group. The analysis in Table 3 showed that there was no confounding between DEP and other patient characteristics.

Esophageal achalasia and hernia along with an anatomical deformed esophagus increase its internal pressure, causing gastroesophageal reflux disease (GERD) and anorexia. As secondary causes of similar symptoms include spondylosis deformans in the elderly and left pneumonectomy for lung cancer [8, 9]. In these literatures, anorexia due to esophageal deviation have been reported. In our study, upper gastrointestinal endoscopy and PH monitoring of the esophagus were not actually performed, but we speculated that a similar mechanism might have exacerbated the side effects of oral adjuvant chemotherapy. In the univariate analysis in Table 4, stomach medicine was more common in high DEP group, which seems to support our hypothesis. In order to benefit from the treatment completion, we believe that it is important to actively consider appropriate pharmacokinetic use of stomach medicine and supportive care, which will lead to maintenance of medication.

This study has several limitations, including its single-center design and retrospective nature. In addition, the small number of patients involved may have influenced results such as ROC analysis, and it can be difficult to determine if the identified factors can be applied to other populations. Further research with more participants is required to resolve this factor, which will be considered in our future studies.

In Conclusion, our retrospective study suggested that postoperative middle thoracic esophageal displacement affected the continuity of oral adjuvant chemotherapy with tegafur-uracil.

Funding

None.

Declaration of Conflicting interests

The authors report no other conflicts of interest.

Ethical Approval

This retrospective study was approved by the institutional review boards at the Shiga University of Medical Science Hospital (approval number R2020-163).

Informed Consent

Ethical approval was not sought for the present study because no identifiable images or

information were used.

Acknowledgments

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Tables

Table 1 Patient characteristics of the study cohort

Variables	
Male sex, n	41
Age＞66 years, n	40
BMI (kg/m^2)	22.7 ± 3.1
Smoker, n	49
Brinkman index	722 ± 640
Tumor diameter (mm)	29.9 ± 10.0
Staging, pathological, n	
p-IA / p-IB / p-II	19 / 29 /10
adeno carcinoma	59
pleural invasion	21
Spirometry, pre-surgery	
VC (mL)	3272 ± 742
%VC (%)	104 ± 14.4
FEV1 (mL)	2371 ± 568
%FEV1 (%)	94.9 ± 25.6
Surgical finding, n	
open thoracotomy	11
RUL/RML/RLL/LUL/LLL	22 / 3 / 13 / 15 /15
subcarinal lymph node dissection	35
Oral tegafur-uracil, n	
capsule	38
initial dose (mg/body), 300 / 400 / 500	20 / 47 / 1
stomach medicine	14
dose reduction	10
discontinuation	27
Distance from the midline to esophagus (mm)	
Th7 level, pre-surgery	14.2 ± 5.7
Th7 level, post-surgery	13.6 ± 7.8
Th10 level, pre-surgery	11.5 ± 5.4
Th10 level, post-surgery	12.6 ± 9.0
Degree of esophageal displacement (mm)	
Th7 level	4.1 ± 5.2
Th10 level	5.0 ± 5.1

BMI, body mass index; VC, vital capacity; FEV1, forced expiratory volume in 1 s; RUL, right upper lobectomy; RML, right middle lobectomy; RLL, right lower lobectomy; LUL, left upper lobectomy; LLL, left lower lobectomy;

Table 2 Patient characteristics in the treatment completion group and the discontinuation group

Variables	Completion group: n=41	Discontinuation group: n=27	*p* -value	
			Univariate	Multivariate
Male sex, n	26	17	0.970	0.664
Age＞66 years, n	22	18	0.286	0.683
BMI (kg/m^2)	22.6 ± 3.4	23.0 ± 2.6	0.618	0.633
Smoker, n	29	20	0.764	0.860
Brinkman index	571 ± 595	361 ± 517	0.713	0.387
Tumor diameter (mm)	29.8 ± 10.1	30.1 ± 10.2	0.917	0.960
Staging, p-IA / p-IB / p-II , n	10 / 25 / 6	9 /14 / 4	0.726*	0.724
Adenocarcinoma	33	26	0.060	0.054
Pleural invasion	13	8	0.856	0.856
Spirometry, pre-surgery				
VC (mL)	3240 ± 759	3320 ± 742	0.668	0.530
%VC (%)	103 ± 14.4	106 ± 14.9	0.504	0.192
FEV1 (mL)	2319 ± 579	2449 ± 563	0.358	0.324
%FEV1 (%)	91.2 ± 23.8	99.4 ± 27.5	0.192	0.191
Surgical finding, n				
open thoracotomy	8	3	0.357	0.355
RUL/RML/RLL/LUL/LLL	9 / 2 / 8 / 5 /3	13/ 1 / 5 / 10 /12	0.193*	0.086
subcarinal lymph node dissection	20	15	0.584	0.777
Usage of tegafur-uracil, n				
capsule	19	11	0.878	0.838
initial dose (mg/body), 300 / 400 / 500	13 / 27 / 1	7 / 20 / 0	0.779*	0.692
stomach medicine	10	4	**0.035**	0.127
Degree of esophageal displacement (mm)				
Th7 level	3.0 ± 3.3	5.8 ± 7.1	**0.026**	**0.046**
Th10 level	4.4 ± 5.8	5.8 ± 6.3	0.287	0.933

BMI, body mass index; VC, vital capacity; FEV1, forced expiratory volume in 1 s; RUL, right upper lobectomy; RML, right middle lobectomy; RLL, right lower lobectomy; LUL, left upper lobectomy; LLL, left lower lobectomy;

*p- value in the Mann-Whitney U test

Table 3 Subgroup analysis of patient characteristics in the two groups classified according to the degree of esophageal displacement

Variables	DEP＞3.0 mm n=31	DEP＜3.0 mm n=37	*p* -value
Male sex, n	20	21	0.647
Age＞66 years, n	16	24	0.527
BMI (kg/m^2)	23.0 ± 3.4	22.6 ± 2.8	0.519
Smoker, n	23	26	0.668
Brinkman index	756 ± 658	693 ± 615	0.782
Tumor diameter (mm)	30.7 ± 10.0	29.3 ± 10.0	0.610
Staging, p-IA / p-IB / p-II , n	7 / 19 / 5	2012/10/5	0.819
Adenocarcinoma	29	30	0.896
Pleural invasion	10	11	0.827
Spirometry, pre-surgery			
VC (mL)	3247 ± 645	3293 ± 814	0.444
%VC (%)	102 ± 13.2	106 ± 15.2	0.390
FEV1 (mL)	2453 ± 510	2301 ± 604	0.651
%FEV1 (%)	94.8 ± 29.6	94.4 ± 21.0	0.256
Surgical finding, n			
open thoracotomy	5	6	0.508
RUL/RML/RLL/LUL/LLL	7 / 2 / 10 / 5 / 7	15 / 1 / 3 / 10 / 8	0.718
subcarinal lymph node	18	17	0.866

DEP, degree of esophageal displacement at Th7 level; BMI, body mass index; VC, vital capacity; FEV1, forced expiratory volume in 1 s; RUL, right upper lobectomy; RML, right middle lobectomy; RLL, right lower lobectomy; LUL, left upper lobectomy; LLL, left lower lobectomy

*p- value in the Mann-Whitney U test

Table 4 Subgroup analysis of treatment outcome in the two groups classified according to the degree of esophageal displacement

Variables	DEP＞3.0 mm n=31	DEP＜3.0 mm n=37	*p* -value	
			Univariate	Multivariate
Stomach medicine, n	10	4	**0.029**	0.414
Dose reduction, n	4	6	0.701	0.882
Discontinuation, reason, n	19	8	**0.020**	0.356
anorexia	9	1	**0.002**	**0.013**
tumor recurrence	4	2	0.528	0.806
hepatobiliary enzyme abnormalities	2	3	0.794	0.921
pneumonia	2	1	0.453	0.292
others	2	1	0.453	0.292

DEP, degree of esophageal displacement at Th7 level

Figure legends

Fig. 1 The red dotted line is the reference line of the mediastinal, which is defined by the line connecting the vertebral body to the tracheal bifurcation at Th7 level (A, C), IVC at Th10 level (B, D). The distance from the reference line to the esophagus was evaluated before and after surgery (yellow arrow). IVC, inferior vena cava

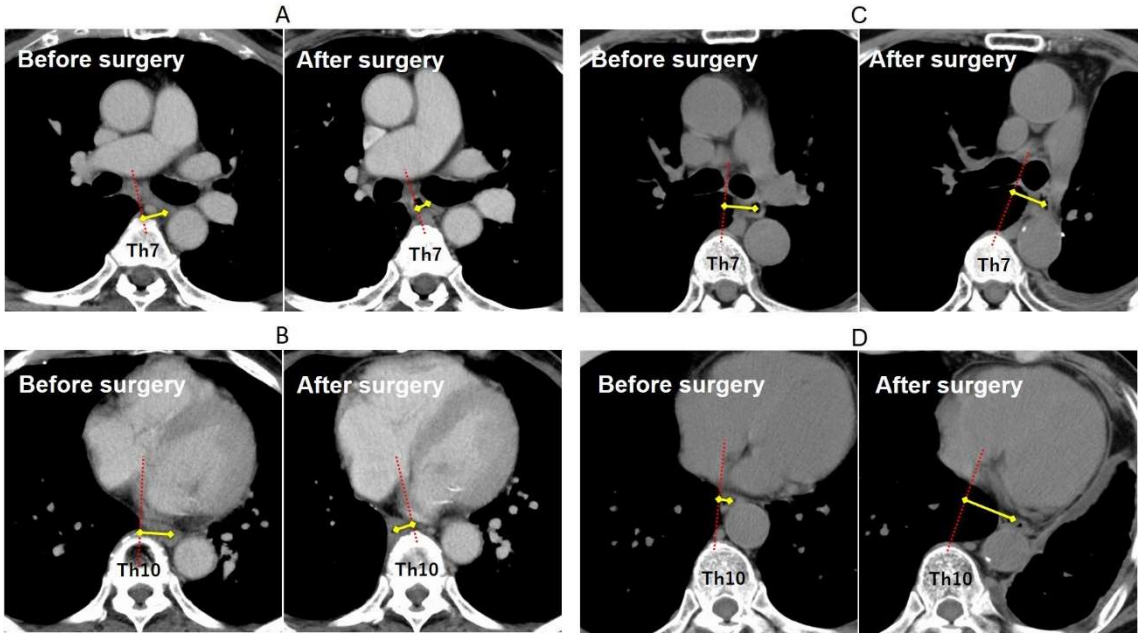

Fig. 2 Overview of study population

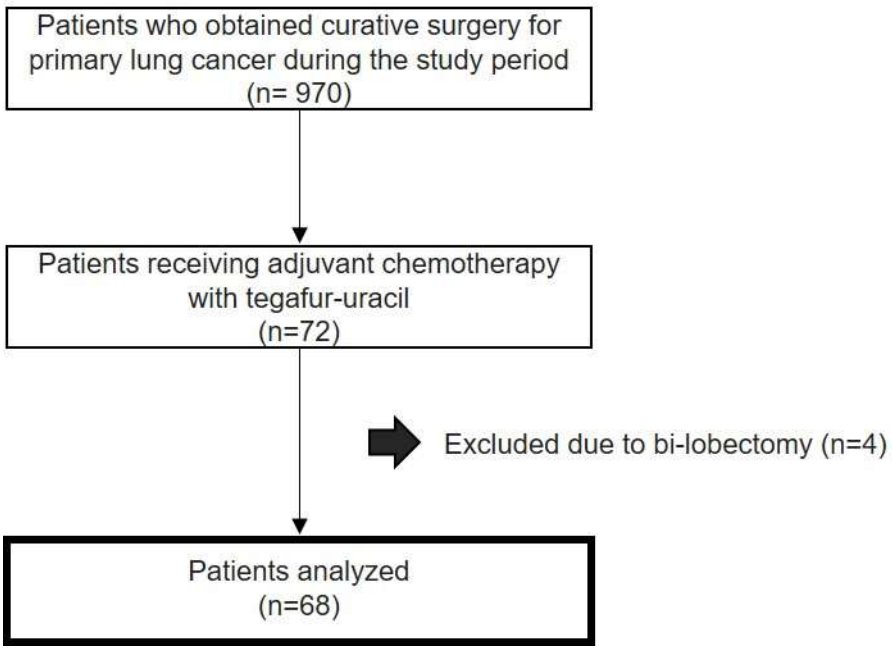

Fig. 3 Kaplan-Meier curves showing OS and RFS A, B: for all patients C, D: for patient groups classified by treatment status. OS, overall survival; RFS, recurrence-free survival