20 months, excellent local control with an objective response rate of 84%, and has demonstrated the safety of the SP with concurrent radiotherapy (SP-RT) [11] for patients with stage III NSCLC.

In contrast, the role of surgery for LA-NSCLC has been controversial, especially due to the heterogeneity of stage III NSCLC patients who have various numbers, stations, or conditions of mediastinal lymph node metastases, modes of tumor invasion to adjacent thoracic structures, or organs such as the great vessels, mediastinum, vertebral body, carina, esophagus, and so on, which might affect the prognosis of such patients. Such diversity of LA-NSCLC patients has precluded the establishment of an optimal treatment strategy.

We have previously reported the feasibility of SP-RT as an induction therapy that can be followed by curative intent resection for 18 patients with potentially resectable LA-NSCLC [12]. In the present study, we retrospectively analyzed the prognostic benefit for a larger number of patients treated with this strategy.

Patients and Methods

We retrospectively reviewed 42 consecutive patients with potentially resectable stage III LA-NSCLC who underwent preoperative induction concurrent chemoradiotherapy using SP-RT followed by curative-intent surgical resection between June 2005 and February 2011 in the Department of Thoracic Oncology, National Kyushu Cancer Center, Japan. The clinical or pathologic stage of the disease was diagnosed based on the general rules for the TNM Classification of Malignant Tumors (6th edition) [13]. Eligible patients had to have cytologically or histologically confirmed clinical stage III NSCLC that was considered to be potentially resectable. The other eligibility criteria were an age between 20 and 80 years, Eastern Cooperative Oncology Group performance status of 0 to 1, absence of previous chemotherapy or radiotherapy, and adequate hematologic, hepatic, and renal function. Patients with standard laboratory tests results, included the following: a leukocyte count of 3.500/μL or greater; a platelet count of 100,000/μL or greater; serum bilirubin level less than 1.5 mg/dL; serum glutamic oxaloacetic transaminase-glutamic pyruvic transaminase levels 100 IU/mL or less, a creatinine level 1.2 mg/dL or less, or a creatinine clearance level of 60 mL/minute or greater, and a blood gas oxygen tension of 60 Torr or greater, or oxygen saturation as measured by pulse oximetry equal to or greater than 95% in room air were considered to be eligible for this treatment. In addition, pulmonary function tests, chest radiography, computed tomography of the chest and the upper abdomen, computed tomography or magnetic resonance imaging of the brain, bronchoscopy using a flexible optical bronchoscope, and a bone scan or fluorodeoxyglucose-positron emission tomography were routinely performed for all patients. Patients who had malignant pleural effusion, malignant pericardial effusion, or a concomitant malignancy or serious comorbidities such as clinically significant cardiac dysfunction, active infection, or neurologic or psychiatric disorders were excluded.

Treatment Schedule

Chemotherapy With SPS-1 (40 mg/m^2 twice a day [b.i.d.]) in the form of 20 mg and 25 mg capsules containing 20 and 25 mg of tegafur, respectively, were taken orally in 2 separate doses from days 1 to 14 and days 22 to 35 as follows: in a patient with a body surface area (BSA) less than 1.25 m^2, 40 mg b.i.d.; for those with a BSA of at least 1.25 m^2 but less than 1.5 m^2, 50 mg b.i.d.; and for those with a BSA greater than 1.5 m^2, 60 mg b.i.d. was administered. Cisplatin, at a dose of 60 mg/m^2, was administered as a 120-minute infusion on days 1 and 22 while the patients were hydrated with 2,500 mL of saline by infusion. In general, this dose and schedule is equivalent of that of patients without radiotherapy. An antiemetic agent was administered at the discretion of each patient's physician.

Radiotherapy (RT)

All patients were treated with a linear accelerator photon beam of 6 MV or more from day 1. The primary tumor and involved nodes received 40 Gy in 2 Gy fractions over a period of 4 weeks. A three-dimensional treatment planning system was used. Radiation doses were specified at the center of the target volume. The delivered 40 Gy/20 fractions included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal to subcarinal lymph nodes. For the primary tumors and the involved lymph nodes that were 1 cm or larger in the shortest diameter, a margin of at least 0.5 cm was added. The contralateral hilum was not included. The treatment of supraclavicular areas was not mandatory, but they were treated when the supraclavicular nodes were involved.

During the concurrent chemoradiotherapy period, chest X-rays, complete blood cell counts, and blood chemistry studies were repeated once a week, and the treatment was interrupted when a grade 4 hematologic or non-hematologic toxicity, including grade 3 to 4 esophagitis or dermatitis, pyrexia of 38°C or greater, or a decrease in the partial pressure of arterial oxygen of 10 Torr or more, compared with that before radiation therapy, occurred.

Surgical Resection

Immediately after completing the induction SP-RT, the patients were assessed for their response to the induction therapy and were restaged. If disease control, such as a complete response, partial response, or stable disease, was achieved a curative intent resection was planned for 3 to 6 weeks after completion of the concurrent chemoradiotherapy. The principles of resection were en bloc removal of the affected lobe or more lung parenchyma with adjacent structure(s) if necessary, with complete hilar and mediastinal lymph nodal dissection.

Evaluation of the Response and Toxicity

The response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors version 1.0 guidelines [14]. The histologic analysis of the tumor was based on the World Health Organization classification for cell types [15]. The toxicity for all patients who received any treatment was assessed and graded by using

the National Cancer Institute Common Terminology Criteria for Adverse Event version 3 [16].

Statistical Analysis

To determine the response rate, the exact binomial confidence interval was calculated. Disease-free survival was defined as the time from the starting date of induction concurrent chemoradiotherapy until disease progression or death, and was calculated for the 39 resected patients. Overall survival was defined as the time from the starting date of induction concurrent chemoradiotherapy until death from any cause. The Kaplan-Meier method was used to describe overall survival and disease-free survival curves. All statistical analyses were done with the IBM SPSS Statistics 18 software package (SPSS Japan, an IBM company, Tokyo Japan).

This retrospective analysis was approved by the Institutional Review Board of the National Kyushu Cancer Center. Written informed consent was obtained from all patients before treatment.

Results

Patient Characteristics

As shown in Table 1, there were 34 males (81.0%) and 8 females (19.0%) with the median age of 59 years (range 42 to 77) who were included in this study. Thirty-three (78.6%) patients showed an ECOG performance status of 0. Twenty-one of the 42 patients (50.0%) had adenocarcinoma, while 12 patients had squamous cell carcinoma (28.6%), 8 had non-small cell carcinoma (unclassified), and 1 had large cell carcinoma. The 26 cStage IIIA patients included 24 cases of T1-3N2 and 2 of T3N1, and the 16 cStage IIIB patients included 13 cases of T4N0-2 and 3 of T2-4N3. All N3 patients had ipsilateral supraclavicular lymph node metastasis. The location of the primary tumor was the upper lobe in 38 patients (90.5%) and other lobes in 4 patients (9.5%).

Table 1. Patient Characteristics That Were Eligible for Induction Treatment

Subject	No.	(%)
No. of patients	42	
Age, years		
Median (range)	59 (47–77)	
Gender		
Male to female	34:8	(81.0:19.0)
ECOG PS		
0:1	33:9	(78.6:21.4)
Histology		
Adenocarcinoma	21	(50.0)
Squamous cell carcinoma	12	(28.6)
Large cell carcinoma	1	(2.4)
Unclassified NSCLC	8	(19.0)
cTN[a]		
T3N1	2	
T1-2N2	20	
T3N2	4	
T4N0	2	
T4N1	5	
T4N2	6	
T2-4N3	3	
cStage[a]		
IIIA	26	(61.9)
IIIB	16	(38.1)
Primary site		
Upper lobe	38	(90.5)
Middle/lower lobe	4	(9.5)

[a] TNM Classification of Malignant Tumors (6th edition).

ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small cell carcinoma.

Induction Treatment

All patients received the planned dose of radiotherapy, and 41 (97.6%) had 2 cycles of chemotherapy as induction treatment. As shown in Table 2, no grade 4 toxicity was observed during this induction therapy. The most frequently observed adverse event was grade 3 leukopenia, but its incidence was less than 10%; the incidence of the other grade 3 adverse events was 2.4% for neutropenia and febrile neutropenia and 4.8% for thrombocytopenia. One patient received 1 cycle of chemotherapy and another patient required a dose reduction of cisplatin [CDDP] during the second cycle of chemotherapy due to grade 2 serum creatinine level elevation. After receiving the induction treatment, 26 (61.9%) of the 42 patients achieved a partial response (PR), and stable disease (SD) was observed in 16 patients (38.1%). No progressive disease was observed.

Surgical Resection

Among the 42 patients, 39 patients (92.9%) were able to undergo surgical resection. One patient proved to be unresectable after thoracotomy because of the left atrial invasion around the inferior pulmonary vein that could not be detected preoperatively, and 2 patients refused surgical treatment at the end of their induction treatment. Among the 39 patients who received the curative intent resection, 27 patients (69.2%) underwent a lobectomy, including 6 sleeve lobectomies and 12 pneumonectomies (5 in right side and 7 in left side) (30.8%) including 10 intrapericardial pneumonectomies. Sixteen of the 39 patients (41.0%) required combined resection of an adjacent structure or organ: the chest wall with rib(s) in 12 cases; combined partial resection of the vertebra in 3 cases; the internal jugular or brachiocephalic vein that required vascular replacement with a vascular prosthesis each in 1 case; the superior vena cava in 1 case; and the left atrium in 1 case (Table 3). Complete resection was performed in all patients. Of the 3 patients with ipsilateral supraclavicular lymph node metastasis, two underwent a systemic mediastinal and supraclavicular lymph nodal dissection via a median sternotomy, and the other one was confirmed to have no metastasis in his supraclavicular lymph nodes by a pathological examination during surgery, and subsequently underwent systemic

Table 2. Toxicities (n = 42); National Cancer Institute Common Terminology Criteria for Adverse Event Version 3

	Grade		Frequency of 3 or 4 (%)
	3	4	
Hematologic			
Leukopenia	3	0	7.1
Neutropenia	1	0	2.4
Thrombocytopenia	2	0	4.8
Anemia	0	0	/
Non-hematologic			
Febrile neutropenia	1	0	2.4
Nausea	0	0	/
Vomiting	0	0	/
Creatinine	0	0	/
AST to ALT	0	0	/
Diarrhea	0	0	/
Stomatitis	0	0	/
Pneumonitis	0	0	/
Esophagitis	0	0	/

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

mediastinal lymph nodal dissection via posterolateral thoracotomy.

Surgical Morbidity and Mortality

The postoperative morbidity in this series of patients were the following: 3 cases each of postoperative bleeding and arterial fibrillation; 2 cases of chylothorax; and 1 each of prolonged air leakage, pulmonary edema, empyema, heart failure, and spinal cord injury. Among these cases, 3 patients underwent re-thoracotomy; 2 for postoperative bleeding and 1 for chylothorax. One patient who had undergone a left upper lobectomy experienced postoperative thoracic empyema without a bronchopleural fistula and died on the 65th postoperative day due to massive intrathoracic bleeding.

Table 3. Type of Resection (n = 39)

Subject	No. (%)
Pneumonectomy	12 (30.8)
Intrapericardial pneumonectomy	10
Lobectomy[a]	27 (69.2)
Sleeve lobectomy	6
Combined resection	16 (41.0)
Site of combined resection (redundant)	
Chest wall (ribs)	12
Vertebra	3
Internal jugular or brachiocephalic vein	2
SVC (replacement with graft)	1
Left atrium	1

[a] One patient with a bilobectomy was included.

SVC = superior vena cava.

Pathologic Findings

Concerning the clinical and pathologic response to induction concurrent chemoradiotherapy using SP-RT in the 39 patients who underwent surgical resection, 9 of the 39 (23.1%) patients showed a complete pathologic response in both the primary tumor and involved lymph nodes, while 6 of these 9 presented clinical PR and 3 clinical SD. Among the other 30 patients (76.9%) with partial pathologic response, 18 showed clinical PR and 12 clinical SD.

Adjuvant Chemotherapy

Twenty-five (64.1%) patients received adjuvant chemotherapy, mainly with cisplatin-based regimens. The regimens were determined by the attending surgeon. Ten of these 25 patients received more than 3 cycles of adjuvant chemotherapy.

Survival and Recurrence

The median follow-up time was 32.0 months. One-, 3-, and 5-year disease-free survival rates in all 39 surgically resected patients were 73.8% (95% CI: 59.95% to 87.7%), 52.0% (95% CI: 34.9% to 69.1%), and 44.0% (95% CI: 26.4% to 61.6%), respectively (Fig 1A). One-, 3- and 5-year overall survival rates were 84.3% (95% CI: 72.7% to 95.9%), 77.4% (95% CI: 63.3% to 91.5%), and 61.7% (95% CI: 42.1% to 81.3%), respectively (Fig 1B). When patients were stratified into those with cStage IIIA versus cStage IIIB, pN0 versus pN1-3, clinical response (ie, PR versus SD and lobectomy versus pneumonectomy), there were no statistically significant differences in either disease-free survival or overall survival (data not shown). However, when patients were stratified by their pathologic response, 3-year disease-free survival rates in the 9 patients with pathologic complete response were 76.2% (95% CI: 47.2% to 100%), while those of the other 30 patients with any pathologic response were 44.5% (95% CI: 24.7% to 64.3%) (Fig 2A). Three-year overall survival rates were 88.9% (95% CI: 68.3% to 100%) in the 9 patients with pathologic complete response, whereas those of the other 30 patients were 74.0% (95% CI: 56.9% to 91.1%) (Fig 2B).

Of the 39 resected patients, recurrence developed in 18 patients. The first site of recurrence in 16 patients was a distant region. The most common first recurrence site was the brain (7 cases) and the lungs (6 cases). Two patients had recurrence in the contralateral mediastinal lymph nodes that was out of the irradiated field during induction treatment. One of the 9 patients who achieved a pathologic complete response experienced recurrence in the contralateral lung.

Comment

The data presented here imply that treatment with concurrent chemoradiotherapy using SP-RT followed by surgery might provide better local disease control and better survival in patients with potentially resectable LA-NSCLC. Because LA-NSCLC is associated with a high risk of local and systemic recurrence of approximately 80% and 60%, respectively [17], combined local and systemic treatments are warranted. In this regard, the

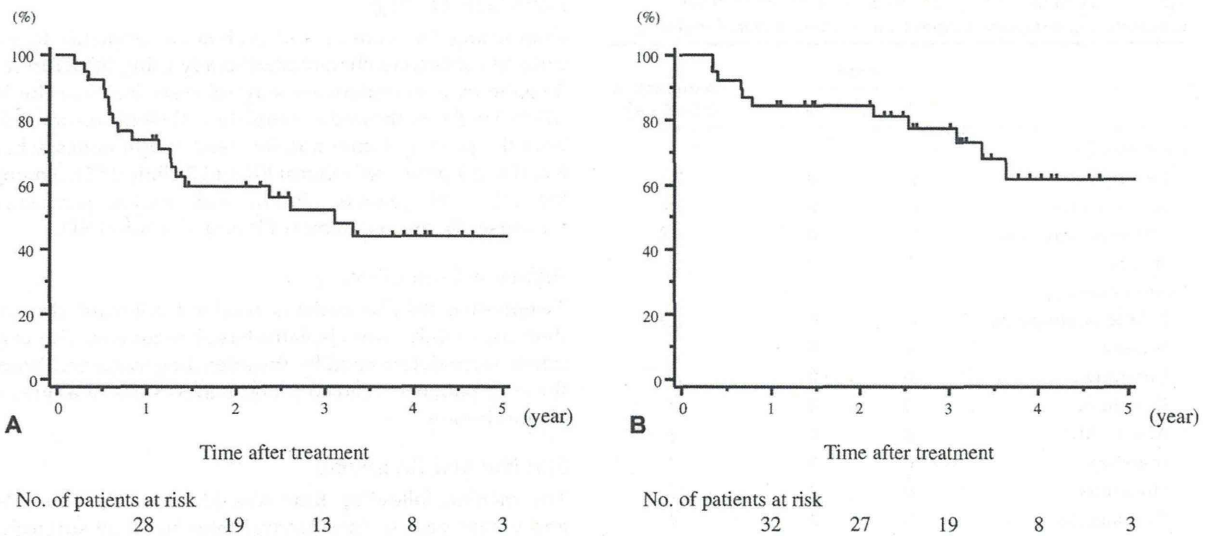

Fig 1. The survival curve of all 39 resected patients. (A) Disease-free survival and (B) overall survival.

optimal treatment strategy for LA- NSCLC is generally considered to be concurrent chemoradiotherapy [18]; however, the most frequent relapse site after concurrent chemoradiotherapy is at a distant region. A possible reason for this type of relapse is that the full-dose chemotherapeutic regimens developed for metastatic-NSCLC in the 1990s cannot be used at the full doses concurrently with radiotherapy due to the associated acute toxicities. Recently, Ichinose and colleagues [11] showed that the combination of full dose SP and concurrent radiotherapy of 60 Gy could be administered with acceptable toxicity, and the treatment with this regimen demonstrated a favorable survival, with a median progression-free survival of 20 months and an ORR of 84%.

Some phase III trials of concurrent chemoradiotherapy with radiation doses ranging from 56 to 66 Gy have shown good response rates of approximately 55% to 80% [19, 20]. In the present study, we observed that 59.5% of patients had a partial response and 40.5% had stable

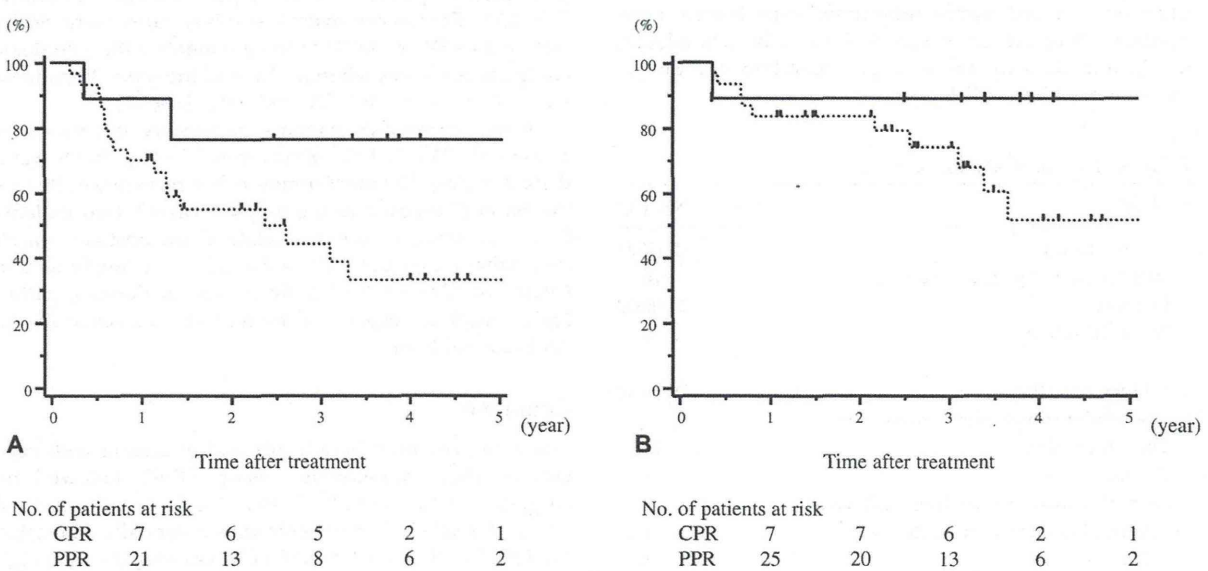

Fig 2. The prognosis of patients stratified by the pathologic response of the resected specimen. Solid line represents patients with complete pathologic response (CPR), while dashed line represents the patients with partial pathologic response (PPR). (A) Disease-free survival; (B) overall survival.

disease after using SP, even with 40 Gy of concurrent radiation therapy. The toxicity of our SP-RT induction treatment was also excellent, without any grade 4 events, which allowed patients to safely undergo the subsequent surgical resection.

Concerning the survival benefit of concurrent chemoradiotherapy for LA-NSCLC, Segawa and colleagues (OLCSG 0007) [19] compared docetaxel plus cisplatin to mitomycin, and vindesine plus cisplatin with concurrent radiotherapy in their phase III study, and reported better 1- and 3-year progression-free survival rates of 53.4% and 24.9%, respectively, and 1- and 3-year overall survival rates of 82.8% and 38.1%, respectively, in the docetaxel plus cisplatin group. Yamamoto and colleagues [20] (WJOG 0105) also compared mitomycin, vindesine plus cisplatin, irinotecan plus carboplatin and paclitaxel plus carboplatin, and demonstrated that a median progression-free survival rate was 9.5 months and a median overall survival was 22.0 months in their docetaxel plus cisplatin group. Focusing on induction concurrent chemoradiotherapy followed by surgery for LA-NSCLC, some phase I and II studies demonstrated promising results in their surgery arm; Friedel and colleagues [21] showed a better median overall survival of 39 months in the subset analysis of their phase II study, and an improved 5-year overall survival rate of 43.1% in patients who underwent surgical resection after induction chemoradiotherapy with carboplatin and paclitaxel with 45 Gy of concurrent radiotherapy for stage III NSCLC compared with those treated without surgical resection, which were 29.6 months and 0%, respectively. Edelman and colleagues [22] reported a good median overall survival of 55.8 months in their series of stage III NSCLC patients with negative mediastinal nodes after induction concurrent chemoradiotherapy using carboplatin and vinorelbine in their phase I/II study. We also previously showed the impact of induction concurrent chemoradiotherapy with cisplatin and UFT on the survival of stage IIIB NSCLC patients who underwent surgical resection, with 1- and 3-year overall survival rates of 82% and 67%, respectively [23].

In their recent report, Albain and colleagues (INT 0139) [24] reported no significant overall survival difference between patients who received induction concurrent chemoradiotherapy with or without surgery; however, the patients who underwent lobectomy showed significant better survival. Additionally, in their resected pT0N0 patients, an excellent median survival of 39 · 8 months was observed. In the present study, a considerably better prognosis was observed; 1-, 3-, and 5-year disease-free survival rates were 73.8%, 52.0%, and 44.0%, respectively (Fig 1A), and 1-, 3-, and 5-year overall survival rates were 84.3%, 77.4%, and 61.7%, respectively (Fig 1B). Our study also indicated that pathologic good responders (ie, patients with complete pathologic response) showed a 3-year disease-free survival rate of 76.2% and 3-year overall survival of 88.9%. We did not evaluate the relationship between the pre-induction and post-induction treatment TNM stage because we believe that one of the important predictive factors for postoperative survival is the pathologic response. That is the reason why we focused on this issue and did not show the correlation between pre-induction and post-induction staging. These results seem to indicate that SP-RT can provide a sufficient systemic dose to prevent occult distant metastasis. In addition, 5-FU is known to have a radiosensitizing effect [25] and S-1 was orally administered for 14 consecutive days twice during the radiotherapy in the present study.

The limitations of the present study are the retrospective nature of the analysis and the relatively small number of patients. We are currently performing a single institutional phase II study of SP-RT as an induction concurrent chemoradiotherapy, followed by surgical resection, for LA-NSCLC patients.

In conclusion, SP-RT followed by surgery may provide a better prognosis for LA-NSCLC patients. Further clinical investigations are warranted.

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INVITED COMMENTARY

To date, 5-fluorouracil (5-FU) has not been utilized in the treatment of non-small cell lung cancer (NSCLC) because of its bioavailability profile, providing lower levels outside the gastrointestinal system. S-1 is an oral fluoropyrimidine drug that combines tegafur, a prodrug of 5-FU, with gimeracil (CHDP) and potassium oxonate (OXO), to increase serum 5-FU levels and minimize gastrointestinal toxicity, respectively. Usually, approximately 80% to 90% of 5-FU administered intravenously is rapidly catabolized by liver dihydropyrimidine dehydrogenase (DPD), and others have also shown high levels of DPD may exist in lung tumors. With S-1, CHDP inhibits both liver and tumor DPD more than 150 times more effectively than uracil and OXO inhibits 5-FU phosphorylation by gastrointestinal mucosal cells. Capecitabine is another oral 5-FU prodrug, but its metabolism is different from that of than tegafur, relying on a final step requiring the enzyme thymidine phosphorylase, which is expressed variably in NSCLC tumors [1].

Although early reports of S-1 in the treatment of NSCLC are now more than a decade old, the clinical use of S-1 has not gained significant traction worldwide yet. Although S-1, in combination with platinum, exhibits antitumor effects in NSCLC as shown in a recent multicenter phase II study (overall response rate 20%, median time to progression 4 months), these results were comparable but not superior to those of other current platinum doublets [2]. This North American study [3], however, used lower doses of S-1 (25 mg/m^2) than in previous studies from Japan in combination with cisplatin at 75 mg/m^2. Yet, S-1 plus platinum demonstrated 50% fewer grade 4 toxicities as compared with other standard platinum doublets for NSCLC. In the present study by Yamaguchi and colleagues [3], S-1 given at 40 mg/m^2 with cisplatin (60 mg/m^2) resulted in a very favorable toxicity profile. The radiosensitizing effects of 5-FU are well known and the higher S-1 dose in the present study likely contributes to the overall results. However, the cohort size here is small, and additional studies will be needed to further explore the optimum dose levels and most effective drug combinations with S-1 for NSCLC.

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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Prognostic Impact of Body Mass Index in Patients with Squamous Cell Carcinoma of the Esophagus

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ABSTRACT

Purpose. To clarify the prognostic impact of body mass index (BMI) in patients with esophageal squamous cell carcinoma (ESCC).

Methods. Two hundred forty-three patients who underwent esophagectomy for ESCC from April 2005 through December 2010 were eligible. Prognoses of the patients were compared between groups stratified according to BMI. We also analyzed the survival difference using propensity score matching to adjust differences in staging and treatment.

Results. Low, normal, and high BMI groups had 35, 177, and 31 patients, respectively. The low BMI group included more advanced cases than did the normal BMI group, while tumor stage was equivalent in the normal and high BMI groups. Disease-free survival of the low and high BMI groups was significantly worse than that of the normal BMI group ($P < 0.0001$ between the low and normal BMI groups; $P = 0.0076$ between the normal and high BMI groups). Disease-free survival of the high BMI group was significantly worse than that of the normal BMI group in the propensity score-matched cohort ($P = 0.0020$). Multivariate analysis in this cohort demonstrated that high BMI was an independent prognostic factor (hazard ratio 2.949, 95 % confidence interval, 1.132–7.683).

Conclusions. High BMI was an independent prognostic factor after curative esophagectomy for ESCC. Although further analysis is required to clarify the influence of overweight on the biological features of ESCC, glucose metabolism may be a therapeutic target for ESCC.

Obesity is a risk factor for several cancers, such as breast, colon, and gynecologic carcinomas.[1] Recently, it has been clarified that obesity not only correlates with carcinogenesis but also influences the prognosis of several cancer patients. For example, obesity correlates with poor prognosis in breast and colon cancers, while favorable prognoses have been reported for obese patients with gastric or renal cancers.[2–5]

The effect of obesity on the prognosis of patients who undergo esophagectomy for esophageal cancer is still unknown. Because increased body mass index (BMI) is also a known risk factor for both Barrett esophagus and esophageal adenocarcinoma, many previous studies focused on adenocarcinoma.[6] Several studies have reported that high BMI does not affect survival.[7,8] However, recent large-scale cohort study demonstrated that obesity is associated with twofold increase in death owing to esophageal adenocarcinoma in patients who never smoked.[9]

As patients with esophageal squamous cell carcinoma (ESCC) were typically had a low BMI because of dysphagia from advanced cancer, little is known about the correlation between obesity and prognosis of ESCC. However, owing to the increasing prevalence of obesity and the development of diagnostic tools facilitating early detection of this disease, the number of overweight patients with ESCC is increasing. In addition, more than 90 % of esophageal cancer patients in Japan have squamous cell carcinoma, which is epidemiologically and clinically

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distinct from adenocarcinoma. Therefore, we sought to clarify the prognostic impact of BMI in patients with ESCC.

In this study, we retrospectively analyzed the correlation between BMI and prognosis of patients who underwent esophagectomy for ESCC.

METHODS

Patients

Two-hundred sixty-eight consecutive patients underwent esophagectomy for esophageal cancer at the Department of Gastroenterological Surgery, Kumamoto University Hospital, from April 2005 through December 2010. Among these, 11 patients with simultaneous head and neck cancers and 14 patients with histologic types of esophageal cancer other than squamous cell carcinoma (12 adenocarcinomas and 2 small cell carcinomas) were excluded. The remaining 243 patients were eligible. The local ethics committee of Kumamoto University approved this study.

Staging of ESCC

Staging of ESCC was based on endoscopy, esophagogram and 18-F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT. Endoscopic ultrasonography (EUS) was performed only when the tumor was limited within the submucosal layer or when tumor invasion into the neighboring organ was suspected by CT. Clinical and pathological findings were classified according to tumor, node, metastasis classification system (7th edition) of the Union for International Cancer Control and the American Joint Committee.[10] When the patient achieved complete response by neoadjuvant treatment, pathologic staging was considered as stage 0.

Collection of BMI Data

Height and weight of all patients were measured at the time of esophagectomy. BMI was calculated by weight (kg) divided by height (m^2). World Health Organization cut points were used to categorize patients as having high BMI ($\geq$25.0 kg/m^2), normal BMI (18.5–24.9 kg/m^2), or low BMI (<18.5 kg/m^2).[11]

Follow-up of Patients

Follow-up of the patients was carried out in our clinic every 3 months until 5 years after surgery. The median follow-up period from the surgery to death or the last visit was 25.7 months. Seven patients were lost to follow-up.

Statistical Analysis

All quantitative data are expressed as mean $\pm$ 1 standard deviation. Statistical analyses were performed by JMP 10 software (SAS Institute, Cary, NC, USA). Differences in clinicopathologic features were determined by Student's *t* test for age, duration of operation, blood loss, number of retrieved nodes, and number of metastatic nodes. Fisher's exact test was used for other variables. Survival rates after esophagectomy were calculated by the Kaplan–Meier method, and statistical significance was determined by the log-rank test. Overall survival was defined as the time from surgery to death resulting from any cause, and disease-free survival was defined as the time from surgery to first recurrence or to death from any cause. The Cox proportional hazard model was used for multivariate analysis of the disease-free survival of 220 patients who underwent R0 esophagectomy.

We created a nonparsimonious logistic regression model to derive a propensity score for patients who belong to the normal and high BMI groups. We matched each patient in the high BMI group with one patient in the normal BMI group. The matched cohort was evaluated for differences in clinicopathologic characteristics between the normal and high BMI groups, using paired *t* test for continuous outcome and McNemar's test for proportions. Survival analysis was performed in this cohort using Kaplan–Meier and Cox proportional hazard model. A P value of <0.05 was considered an indication of statistical significance.

RESULTS

The low, normal, and high BMI groups had 35, 177, and 31 patients, respectively. Differences in clinicopathologic factors among the groups stratified by BMI are summarized in Table 1. Variables were compared between the low and normal BMI groups and between the normal and high BMI groups. There were more women in the low BMI group than in the normal BMI group. Clinical stage of cancer was significantly greater in the low BMI group than in the normal BMI group. Cardiac comorbidity was significantly lesser in the low BMI group than in the normal BMI group. The prevalence of diabetes mellitus was greater in the high BMI group than in the normal BMI group. Clinical stage was comparable between the normal and high BMI groups. Type of esophagectomy, operative time, blood loss, and the incidence of postoperative complications were comparable among the groups. The number of retrieved nodes was significantly less in the low BMI group than in the normal BMI group. Pathologic stage was significantly higher in the low BMI group than in the normal BMI group, and R0 resection was less frequent in the low BMI group than in the normal BMI group. In contrast, pathologic stage was

comparable between the normal and high BMI groups, and no significant difference was observed in the number of retrieved nodes or R0 resection rate between these two groups. Percentage of patients who underwent postoperative chemotherapy was comparable among the groups. These results suggest that there were more advanced cases in the low BMI group than in the normal BMI group, while tumor stage was equivalent in the normal and high BMI groups.

Overall survival and disease-free survival are provided in Fig. 1. Overall survival of both the low BMI group and the high BMI group were significantly worse than that of the normal BMI group ($P = 0.0003$ between the low and normal BMI groups; $P = 0.0014$ between the normal and high BMI groups). Similarly, disease-free survival of the low and high BMI groups was significantly worse than that of the normal BMI group ($P < 0.0001$ between the low and normal BMI groups; $P = 0.0076$ between the normal and high BMI groups).

In order to evaluate influence of preoperative treatment on BMI, we compared BMIs measured before and after treatment (Supplemental Fig. 1). We collected pretreatment BMI data of 81 among 96 patients who underwent preoperative treatment, while we missed the data of 15 cases who underwent preoperative treatment in the other institutes. Significant decrease in BMI was observed in patients who underwent definitive chemoradiotherapy, although there was no significant change in BMI during neoadjuvant treatment. When we compared outcomes among groups stratified by pretreatment BMI, survival of the high BMI group was also significantly worse than that of the normal BMI group.

In order to control the differences in stage of disease and treatment types between the normal BMI group and the high BMI group, propensity score-matching cohort was selected. There were 27 pairs in the cohort. Characteristics of patients are shown in Table 2. There was no significant difference in the stage of disease and types of treatment between the pairs. Disease-free survival of the high BMI group was also significantly worse than that of the normal BMI group in this cohort (Fig. 2, $P = 0.020$). Cox proportional hazard model revealed that high BMI was an independent prognostic factor in this cohort (Table 3, hazard ratio 2.949, 95 % confidence interval, 1.132–7.683).

DISCUSSION

In this study, we clarified that both undernutrition and overweight negatively affected prognosis for patients with ESCC. Advanced disease was the explanation for poor prognosis in the low BMI group, whereas biologically aggressive tumors might be responsible for poor prognosis in the high BMI group. Several authors have reported that an elevated BMI did not reduce survival of patients who underwent esophagectomy for cancer.[6–8, 12,13] However, recent large-scale cohort study demonstrated that obesity among never smokers was independently associated with poor prognosis in patients with esophageal adenocarcinoma.[9] Subjects of these previous studies are mainly adenocarcinoma, and even in the studies which targeted both histologic subtypes, percentage of patients with ESCC was as low as 10–47 %. Therefore, this is the first report to demonstrate the prognostic impact of BMI in ESCC.

More advanced diseases, more salvage esophagectomies after definitive chemoradiotherapy, fewer retrieved lymph nodes, and fewer R0 resections were features of the low BMI group. These findings indicate that advanced cancer is the obvious reason for poor prognosis in this group. Advanced esophageal cancer is often accompanied by malignant stricture and thus can result in poor nutrition. In addition, preoperative treatment for advanced cancer may induce malnutrition. Han-Geurts et al.[14] reported that nutritional parameters are significantly worse in patients with neoadjuvant treatment compared to those who receive no such treatment. In particular, mucosal injuries of the upper digestive tract induced by chemoradiotherapy can decrease caloric intake. The reason of the fewer retrieved lymph nodes was that significantly more salvage surgeries were included in this group. Salvage esophagectomy is well known as high risk surgery, and therefore preventive lymph node dissection is usually minimized to decrease postoperative morbidity and mortality in this type of surgery.[15]

The normal and high BMI groups, however, did not differ in preoperative factors, except the prevalence of diabetes. Although tumor stage and surgical curability were similar between the groups, prognosis was significantly worse in the high BMI group. In addition, disease-free survival of the high BMI group was also significantly worse than that of the normal BMI group in the propensity score-matching cohort. These findings strongly suggest that tumors in overweight patients are more aggressive than those in patients of normal weight. We tried to identify morphologic difference between the high BMI group and the others but failed to find any differences.

Obesity has been known for many years to increase the risk of type 2 diabetes and is itself associated with cancer risk.[1] In this study, the prevalence of diabetes was significantly higher in the high BMI group (16.1 %) than in the normal (7.9 %) and low (2.9 %) BMI groups. Epidemiological studies have reported that patients with diabetes who develop cancer have a worse prognosis after treatment with chemotherapy or surgery and have greater mortality than do those without diabetes.[16,17] Both hyperglycemia and hyperinsulinemia induced by type 2 diabetes have been

TABLE 1 Differences in clinicopathologic factors among the groups stratified by BMI

Characteristic	Variable	Low BMI	Normal BMI	High BMI	*P* value	
		($n = 35$)	($n = 177$)	($n = 31$)	L vs. N	N vs. H
Age	Mean ± SD	64.9 ± 9.6	66.2 ± 8.7	68.6 ± 8.0	0.43	0.14
Sex	Male	26 (74.3)	160 (90.4)	28 (90.3)	0.0079	0.99
	Female	9 (25.7)	17 (9.6)	3 (9.7)		
BMI	Mean ± SD	17.3 ± 1.2	21.7 ± 1.7	26.5 ± 1.1	<0.0001	<0.0001
Location	Upper	6 (17.1)	26 (14.7)	4 (12.9)	0.72	0.97
	Middle	15 (42.9)	89 (50.3)	16 (51.6)		
	Lower	14 (40.0)	62 (35.0)	11 (35.5)		
cT	1	7 (20.0)	88 (49.7)	11 (35.5)	0.0044	0.23
	2	6 (17.1)	27 (15.3)	9 (29.0)		
	3	18 (51.4)	56 (31.6)	10 (32.3)		
	4	4 (11.4)	6 (3.4)	1 (3.2)		
cN	0	11 (31.4)	91 (51.4)	14 (45.2)	0.11	0.81
	1	19 (54.3)	61 (34.5)	13 (41.9)		
	2	4 (11.4)	23 (13.0)	4 (12.9)		
	3	1 (2.9)	2 (1.1)	0		
cStage	IA	4 (11.4)	70 (39.5)	8 (25.8)	0.022	0.63
	IB	2 (5.7)	10 (5.6)	4 (12.9)		
	IIA	5 (14.3)	12 (6.8)	2 (6.5)		
	IIB	6 (17.1)	24 (13.6)	6 (19.4)		
	IIIA	11 (31.4)	39 (22.0)	8 (25.8)		
	IIIB	2 (5.7)	14 (7.9)	2 (6.5)		
	IIIC	5 (14.3)	8 (4.5)	1 (3.2)		
	IV	0	0	0		
Neoadjuvant treatment	None	17 (48.6)	113 (63.8)	17 (54.8)	0.027	0.68
	CT	5 (14.3)	37 (20.9)	9 (29.0)		
	CRT	4 (11.4)	9 (5.1)	1 (3.2)		
	dCRT	9 (25.7)	18 (10.2)	4 (12.9)		
Comorbidity	Present	19 (54.3)	69 (39.0)	9 (29.0)	0.093	0.29
Pulmonary	Present	5 (14.3)	24 (13.6)	4 (12.9)	0.91	0.92
Cardiac	Present	3 (8.6)	57 (32.2)	13 (41.9)	0.0046	0.29
Hepatic	Present	2 (5.7)	12 (6.8)	4 (12.9)	0.82	0.24
Diabetes	Present	1 (2.9)	10 (5.6)	5 (16.1)	0.50	0.038
CVD	Present	1 (2.9)	14 (7.9)	2 (6.5)	0.29	0.78
Type of esophagectomy	TT	31 (88.6)	168 (92.7)	27 (87.0)	0.64	0.12
	IL	2 (5.7)	8 (4.5)	4 (12.9)		
	TH	2 (5.7)	5 (2.8)	0		
Duration of operation (min)	Mean ± SD	533 ± 146	523 ± 122	563 ± 193	0.67	0.13
Blood loss (g)	Mean ± SD	568 ± 388	540 ± 435	676 ± 328	0.72	0.098
Postoperative complication	Present	13 (37.1)	50 (28.2)	9 (29.0)	0.92	0.94
Pulmonary	Present	8 (22.9)	33 (18.6)	8 (25.8)	0.64	0.33
Anastomotic leak	Present	8 (22.9)	27 (15.3)	6 (19.4)	0.32	0.60
Recurrent nerve palsy	Present	7 (20.0)	34 (19.2)	8 (25.8)	>0.99	0.47
No. of retrieved nodes	Mean ± SD	36.2 ± 22.4	44.4 ± 20.5	40.4 ± 18.3	0.033	0.30
No. of metastatic nodes	Mean ± SD	1.9 ± 2.6	1.6 ± 2.8	2.0 ± 2.8	0.67	0.47
pT	0	2 (5.7)	5 (2.8)	3 (9.7)	0.0002	0.22
	1	9 (25.7)	98 (55.4)	12 (38.7)		
	2	3 (8.6)	28 (15.8)	4 (12.9)		
	3	16 (45.7)	43 (24.3)	11 (35.5)		
	4a	2 (5.7)	1 (0.6)	0		
	4b	3 (8.6)	2 (1.1)	1 (3.2)		