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ORIGINAL ARTICLE

Non-small cell lung cancer with pathological complete response: predictive factors and surgical outcomes

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Abstract

Objectives When induction therapy followed by surgery for locally advanced non-small cell lung cancer results in pathological complete response, the prognosis is excellent; however, relapses can occur. We analyzed the predictive factors for achieving pathological complete response and reviewed the clinicopathological features and surgical outcomes of locally advanced non-small cell lung cancer with pathological complete response.

Methods Between March 2005 and January 2015, 145 resections after induction therapy for locally advanced non-small cell lung cancer were performed; 38 cases achieved pathological complete response. Predictive factors for achieving pathological complete response were analyzed, and the clinicopathological features and surgical outcomes of 38 cases with pathological complete response were retrospectively reviewed.

Results Of 145 patients, 98 underwent induction chemoradiation and 47, induction chemotherapy. Squamous cell carcinoma occurred most frequently ($n=64$), followed by adenocarcinoma ($n=53$). Only squamous cell carcinoma was positively associated with achieving pathological complete response ($p=0.009$). Of 38 patients with pathological complete response, 33 were men and the mean age was 67.0 ± 6.3 years; the clinical stages were IIA ($n=3$), IIB ($n=2$), IIIA ($n=26$), and IIIB ($n=3$). One patient died within 30 days post-surgery (2.6%). Eight recurrences occurred during the follow-up period; brain metastasis occurred most frequently. The 5-year overall and recurrence-free survival rates were 79.5% and 72.6%, respectively.

Conclusions Squamous cell carcinoma was identified as a positive predictive factor for achieving pathological complete response. Among patients undergoing lung cancer surgery after induction therapy with pathological complete response, brain metastasis occurred most frequently.

Keywords Pathological complete response · Induction therapy · Lung cancer · Surgical outcome · Squamous cell carcinoma

Introduction

Despite the advances of various treatments such as chemotherapy, including molecular targeted drugs and immunotherapy, surgical techniques, and perioperative management, lung cancer remains one of the leading causes of deaths worldwide. Specifically, the treatment of locally advanced non-small cell lung cancer (NSCLC) is still challenging. For locally advanced NSCLC, treatment options include induction therapy followed by surgical resection [1–5]. Particularly, when pathological complete response (pCR) is achieved after induction therapy, excellent surgical outcomes are expected [5–7]. On the contrary, cases of recurrent NSCLC are occasionally observed in NSCLC patients with pCR. Although a small number of studies have been

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performed on recurrences of locally advanced NSCLC with pCR after induction therapy [8–10], little is known about predictive factors for achieving pCR, and the surgical outcomes, pattern of recurrence, and prognosis of locally advanced NSCLC with pCR after induction therapy remain unclear. Here, we retrospectively reviewed resected NSCLC cases after induction therapy and analyzed the predictive factors for achieving pCR by comparing the cases with pCR to those without pCR. In addition, we reviewed the clinicopathological features, surgical outcomes, and prognosis of NSCLC with pCR. Moreover, in the cases of recurrent NSCLC with pCR, we report the pattern of recurrence and the treatments after recurrence.

Materials and methods

Patients

Between March 2005 and January 2015, 2006 surgical resections for NSCLC and 145 surgical resections after induction therapy for locally advanced NSCLC were performed in Kurashiki Central Hospital. Of the 145 cases, 38 (26.2%) were NSCLC that underwent surgical resection after induction therapy and achieved pCR. The staging of NSCLC before and after induction therapy was performed based on computed tomography (CT) imaging, and if available, ^{18}F-fluorodeoxyglucose positron emission tomography or brain magnetic resource imaging (MRI) according to the 7th edition of the tumor node metastasis (TNM) classification of lung cancer [11]. Mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration was not routinely performed for assessments of mediastinal lymph nodes. First, we analyzed the predictive factors for achieving pCR by reviewing the 145 cases that underwent induction therapy. Second, we reviewed the 38 cases of NSCLC that achieved pCR and retrospectively analyzed the clinicopathological features, surgical outcomes, and prognosis of these cases by comparing them with the cases that did not achieve pCR. Third, in cases of recurrent NSCLC with pCR, the pattern of recurrence and treatments after recurrence was reviewed.

The observation period was defined as the date of surgery to the date of last follow-up or death. The observation period of recurrent-free survival was defined as the date of surgery to the date of last follow-up, recurrence, or death from causes other than recurrent NSCLC. Follow-up was censored in December 2017. The median observation period was 1637 days (range, 18–4403 days). This study was approved by the Kurashiki Central Hospital Review Board. The requirement of informed consent from each patient was waived due to the retrospective nature of the data.

Induction therapy and adjuvant therapy

Induction therapy was considered for cN2-NSCLC cases, for cases of centrally located NSCLC and for NSCLC cases with suspicion of adjacent organ invasion to secure a safety surgical margin. The type of induction therapy was determined by the cancer board that consisted of thoracic surgeons, radiation oncologists, and thoracic oncologists. As an induction therapy, induction chemoradiation was mainly considered, but in cases of having interstitial pneumonia or when the radiation field was so large that the dose of the lung was too high, induction chemotherapy was chosen [12].

Whether adjuvant therapy was to be performed was determined based on the patient's postoperative condition by the cancer board. The type of adjuvant therapy was also determined by the cancer board.

Statistical analyses

All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [13]. The data were evaluated with Student's t test, and Fisher's exact test was used for 2-group analysis. For multivariate analysis, a logistic regression model was used. Actuarial survival rates were calculated using the Kaplan–Meier method. All values were expressed as mean ± standard deviations. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

Patients undergoing induction therapy followed by surgery

Of 145 patients undergoing induction therapy followed by surgery, 98 resections were performed after induction chemoradiation and 47 after induction chemotherapy. The mean age was 67.1 ± 8.3 years, and 109 were men. Squamous cell carcinoma accounted for 64 cases, adenocarcinoma for 53 cases, and 28 cases were other histologic types. The mean tumor size was 42.8 ± 19.1 mm, and the clinical stage of NSCLC consisted of stage IIA ($n = 15$), IIB ($n = 18$), IIIA ($n = 106$), and IIIB ($n = 6$). Of 106 patients with stage IIIA NSCLC, 90 had cN2 disease.

The most common induction chemotherapy regimen was the combination of carboplatin and paclitaxel ($n = 130$). Other regimens included the combinations of carboplatin and docetaxel ($n = 3$), carboplatin and gemcitabine ($n = 3$),

and cisplatin and pemetrexed ($n=2$). Among the 98 patients that received induction chemoradiotherapy, 29 patients received 30 Gy, 39 received 40 Gy, 3 received 45 Gy, and 27 received 50 Gy.

Patients achieving pathological complete response after undergoing induction therapy followed by surgery

The mean age of the 38 patients that achieved pCR was 67.0 ± 6.3 years, and 33 patients were men. 36 patients had a history of smoking (94.7%); the median Brinkman index was 940 (range, 0–4000), and the mean tumor size was 42.0 ± 17.7 mm. The histology of the lung cancer was as follows: squamous cell carcinoma ($n=23$), adenocarcinoma ($n=9$), and other types ($n=6$). There were no significant differences in age, sex, tumor size, clinical stage of NSCLC, or tumor histology between the patients who achieved pCR and those who did not (Table 1). 25 patients (65.8%) were diagnosed as having cN2 disease.

Among 38 cases with pCR, induction chemoradiation was performed in 30 patients and induction chemotherapy was performed in 8 patients. The regimen of chemotherapy was 2 courses of carboplatin and paclitaxel in all but 1 patient; in the remaining patient, it was 2 courses of cisplatin and etoposide. The radiation dose change over time in our institution; 11 patients received 30 Gy, 13 received 40 Gy, and 6 received 50 Gy. Concerning the adjuvant therapy, adjuvant chemoradiation was performed in 1 patient, and adjuvant chemotherapy was performed in 24 patients. The regimen of chemotherapy was the same as the induction therapy.

Table 1 Patient characteristics of 145 patients with NSCLC undergoing induction therapy followed by surgery

Factor	Not pCR ($n=107$)	pCR ($n=38$)	p value
Age (years)	67.1 ± 9.0	67.0 ± 6.3	0.939
Sex			0.079
Male	76 (71.0%)	33 (86.8%)	
Female	31 (29.0%)	5 (13.2%)	
Tumor size (mm)	43.1 ± 19.7	42.0 ± 17.7	0.777
Clinical stage of NSCLC			0.883
Stage IIA	12 (11.2)	3 (7.9)	
Stage IIB	14 (13.1)	4 (10.5)	
Stage IIIA	77 (72.0)	29 (76.3)	
Stage IIIB	4 (3.7)	2 (5.3)	
Histology (%)			0.059
Squamous cell carcinoma	41 (38.3)	23 (60.5)	
Adenocarcinoma	44 (41.1)	9 (23.7)	
Others	22 (20.6)	6 (15.8)	
Induction therapy (%)			
Induction chemoradiation	68 (63.6)	30 (78.9)	0.107
Induction chemotherapy	39 (36.4)	8 (21.1)	

There were no significant differences between age, sex, tumor size, clinical stage of NSCLC, and histology in patients with NSCLC with and without pCR

NSCLC non-small cell lung cancer, *pCR* pathological complete response

Predictive factors for achieving pathological complete response

Of 145 patients undergoing induction therapy followed by surgery for locally advanced NSCLC, pCR was achieved in 38 patients. In univariate analysis, squamous cell carcinoma was identified as a positive predictive factor for achieving pCR with an odds ratio of 2.45 (95% confidence interval [CI]: 1.08–5.69, $p=0.023$), whereas other factors such as radiation or tumor size were not associated with pCR (Table 2).

Surgical procedures

Of 38 patients with NSCLC who achieved pCR, 32 underwent lobectomy after induction therapy, while 6 patients underwent pneumonectomy. Complete resection of the tumor was achieved in all 38 patients. Combined resection was performed in 6 patients: with the chest wall ($n=2$), with the superior vena cava ($n=1$), with the esophageal muscle ($n=1$), with the pericardium ($n=1$), and with the parietal pleura ($n=1$). The 32 lobectomies included right upper lobectomies with bronchial sleeve ($n=5$) and right upper lobectomies with pulmonary arterioplasty ($n=2$). Regarding the surgical mortality, there was 1 30-day mortality case (2.6%). This patient died from acute respiratory distress syndrome (ARDS) 18 days postoperatively.

Table 2 Univariate analysis of predictive factors associated with achieving pCR in patients with NSCLC (expressed as odds ratios with 95% confidence intervals)

Conditions	Odds ratio in univariate analysis (95% CI)	p value
Squamous cell carcinoma	2.45 (1.08–5.69)	0.023
Radiation	2.14 (0.85–5.95)	0.107
Tumor size (> 40 mm)	0.72 (0.31–1.62)	0.450
Clinically suspected as N2	1.45 (0.63–3.52)	0.437
Age (> 70 years)	0.78 (0.33–1.76)	0.568

CI confidence interval, *pCR* pathological complete response, *NSCLC* non-small cell lung cancer

Recurrent cases

Of 38 patients with NSCLC who had achieved pCR, recurrences of NSCLC occurred in 8 patients (21.1%) during the follow-up period. 7 out of 8 patients underwent surgical resection after induction chemoradiation, while the remaining 1 patient underwent surgical resection after induction chemotherapy. 5 of 8 recurrences were distant metastases, 2 were locoregional recurrences which consisted of ipsilateral lung metastases ($n=2$), and the remaining 1 was both distant and locoregional. Distant metastases consisted of brain metastases ($n=3$), contralateral lung metastasis ($n=1$), both brain and contralateral lung metastasis ($n=1$). Both distant and locoregional metastases consisted of mediastinal lymph node metastasis and vertebral metastasis ($n=1$). Regarding treatments after recurrence, surgical resection and/or radiation therapy followed by systemic chemotherapy were performed for brain metastases. For ipsilateral lung metastasis in 1 patient, surgical resection followed by chemoradiotherapy was performed, while in the other patient, best supportive therapy was performed due to the deterioration of the patient's general condition. Consequently, 4 patients died from the advance of NSCLC; in contrast, the remaining 4 patients were alive with cancer at the end of the study period (Table 3).

Prognosis

Compared with the patients with NSCLC who did not achieve pCR ($n=107$), the patients with NSCLC who did achieve pCR ($n=38$) had significantly better overall and recurrence-free survival rates ($p=0.003$ and $p<0.001$, respectively). The 5-year overall survival rates of patients with and without pCR were 79.5% (95% CI: 61.3–89.8%) and 58.1% (95% CI: 47.6–67.2%), respectively, and the 5-year recurrence-free survival rates of patients with and without pCR were 72.6% (95% CI: 54.9–84.3%) and 43.1% (95% CI: 33.5–52.4%), respectively (Fig. 1).

We also compared overall survival rate and recurrence-free survival rate between patients with and without squamous cell carcinoma ($n=64$ and $n=81$, respectively). In overall survival, there was no significant difference between patients with and without squamous cell carcinoma (5-year overall survival rate: 61.4% [95% CI: 48.1–72.3%] vs 65.3% [95% CI: 52.8–75.2%], respectively, $p=0.116$, Fig. 2a). Similarly, there was no significant difference in recurrence-free survival (5-year recurrence-free survival rate: 53.5% [95% CI: 40.3–65.0%] vs 48.6% [95% CI: 37.3–59.1%], respectively, $p=0.759$ Fig. 2b).

Then, we compared overall survival and recurrence-free survival in terms of radiation therapy. Among 145 patients, there was no significant difference in overall survival between patients receiving ($n=98$) and not receiving ($n=47$) radiation therapy (5-year overall survival rate: 66.8% [95% CI: 55.8–75.7%] vs 57.2% [95% CI: 41.2–70.3%], respectively, $p=0.141$, Fig. 3a). As well as overall survival, there was no significant difference in recurrence-free survival (5-year recurrence-free survival rate: 51.8% [95% CI: 41.2–61.4%] vs 48.6% [95% CI: 33.7–62.0%], respectively, $p=0.482$, Fig. 3b). Similarly, we compared overall survival and recurrence-free survival among patients with squamous cell carcinoma, since, as mentioned above, squamous cell carcinoma was identified as a positive predictive factor in univariate analysis. In overall survival, there was no significant difference between patients receiving ($n=43$) and not receiving ($n=21$) radiation therapy (5-year overall survival rate: 61.3% [95% CI: 44.5–74.4%] vs 61.2% [95% CI: 37.1–78.4%], respectively, $p=0.582$, Supplemental Fig. 1a). In addition, there was no significant difference in recurrence-free survival (5-year overall survival rate: 52.1% [95% CI: 35.8–66.0%] vs 56.1% [95% CI: 32.5–74.3%], respectively, $p=0.962$, Supplemental Fig. 1b).

Finally, we compared overall survival rate among the 38 patients that achieved pCR. There was no significant difference in the 5-year overall survival between patients receiving induction chemoradiation or induction chemotherapy (73.7% [95% CI: 51.9–86.7%] and 100.0% [95% CI: 100–100%], respectively, $p=0.465$).

Discussion

In this study, several important findings were revealed. First, squamous cell carcinoma was found to be positively associated with achieving pCR. Second, although the number of cases was small, there were some cases of lung cancer recurrence, and brain metastasis occurred most frequently. Finally, the prognosis of the cases of NSCLC with pCR was excellent, and surgical resections after induction therapy were performed relatively safely.

For the treatment of locally advanced NSCLC, surgical resection after induction therapy is widely performed with satisfactory outcomes [1–5, 14–18]. Of cases treated with surgical resection after induction therapy, an improved prognosis was reported for the cases achieving downstaging or better pathological responses [5, 17, 18]. Moreover, when pCR is achieved after induction therapy, an excellent prognosis is expected. We identified squamous cell carcinoma as a positive predictive factor for achieving pCR, which was rarely reported. The mechanisms underlying the association between squamous cell carcinoma and pCR remain uncertain, but we speculate that the clinicopathological differences between squamous cell carcinoma and adenocarcinoma play a role [5, 19–24]. In contrast, when we compared overall survival and recurrence-free survival between patients with and without squamous cell carcinoma,

Table 3 Characteristics of 8 cases of non-small cell lung cancer recurrence after surgical resection

Sex	Age	Brinkmann Index	Histology	cStage	cTNM	Tumor size (mm)	Radiation dose (Gy)	Surgical resection	Complication	Adjuvant therapy	Pattern of recurrence	Site of recurrence	Timing of recurrence after surgery	Therapy after recurrence	Prognosis
Male	69	1920	Sq	IIIA	cT2aN2M0	27	30	Pneumonectomy	Chylothorax (G3b) Empyema without BPF (G3b)	Performed	Distant metastasis	Contralateral lung metastasis	38 months	Surgical resection of metastasis + chemotherapy	Death from cancer 52 months after surgery
Male	76	510	Ad	IIIA	cT2aN2M0	45	30	Lobectomy	None	Performed	Distant metastasis	Brain metastasis	5 months	Radiation (whole brain) + chemotherapy	Death from cancer 11 months after surgery
Male	71	840	Sq	IIIA	cT3N2M0	64	30	Pneumonectomy	Tachyarrhythmia (G2)	Not performed	Distant metastasis	Brain metastasis and contralateral lung metastasis	4 months	Radiation (SRT) + chemotherapy	Death from cancer 7 months after surgery
Female	66	1840	Other	IIA	cT2aN1M0	35	40	Lobectomy with angioplasty	Pneumonia (G2) Hypoxemia (G2)	Performed	Locoregional recurrence	Ipsilateral lung metastasis	63 months	Surgical resection of metastasis + chemoradiotherapy	Alive 82 months after surgery
Male	74	260	NSCLC	IIIA	cT2aN2M0	34	0	Lobectomy	Air leak (G3)	Performed	Locoregional recurrence + Distant metastasis	Mediastinal lymph node and vertebral metastasis	18 months	Chemotherapy	Alive 48 months after surgery
Female	67	0	Ad	IIIA	cT4N1M0	40	40	Lobectomy	None	Performed	Distant metastasis	Brain metastasis	17 months	Surgical resection of metastasis + radiation	Alive 35 months after surgery

Table 3 (continued)

Sex	Age	Brinkmann Index	Histology	cStage	cTNM	Tumor size (mm)	Radiation dose (Gy)	Surgical resection	Complication	Adjuvant therapy	Pattern of recurrence	Site of recurrence	Timing of recurrence after surgery	Therapy after recurrence	Prognosis
Female	71	820	Sq	IIIA	cT3N1M0	37	40	Lobectomy	Hypoxemia (G2)	Not performed	Locoregional recurrence	Ipsilateral lung metastasis	25 months	Best supportive care	Death from cancer 31 months after surgery
Male	54	840	Sq	IIIA	cT3N2M0	14	40	Sleeve lobectomy	Drug fever (G2)	Not performed	Distant metastasis	Brain metastasis	2 months	Surgical resection of metastasis and chemo/radiation therapy	Alive 35 months after surgery

Ad adenocarcinoma, *NSCLC* non-small cell lung cancer, *Sq* squamous cell carcinoma, *SRT* stereotactic radiotherapy

we found that there were no significant differences in both overall survival and recurrence-free survival. From these results, we speculate that some patients with squamous cell carcinoma did responded well to induction therapy, but as the prognoses of patients with squamous cell carcinoma undergoing surgical resection after induction therapy was greatly influenced by the distant metastases, no significant differences were observed in either overall and recurrence-free survival.

In this study, the surgical outcomes of resection after induction therapy were acceptable with a low 30-day mortality rate (2.6%) [25]. Additionally, since the 5-year overall survival rate in all 38 cases of locally advanced NSCLC with pCR was 79.5%, the prognosis of patients with NSCLC who achieved pCR was excellent. In the present study, it was showed that both overall survival and recurrence-free survival rates were significantly better in the patients with pCR than in the patients without pCR.

Conversely, although the prognosis of NSCLC patients who achieved pCR was excellent, a few patients experienced recurrences of NSCLC after surgery. The majority of recurrences were distant metastases, and the most frequent site of recurrence was the brain. Most likely, the blood–brain barrier played a role in preventing cytotoxic anticancer agents from reaching the brain [5].

Regarding the regimen of chemotherapy, as in other studies [14, 17], we usually administered carboplatin combined with paclitaxel [12]. Although the adverse effects of this regimen were not mentioned here, completion of induction therapy was achieved in all our patients. This chemotherapy regimen is therefore suitable for induction therapy.

For the induction therapy, we prefer induction chemoradiation to induction chemotherapy, since it was reported that the local control of locally advanced NSCLC after induction chemoradiation was superior to induction chemotherapy [12, 26, 27]. In this study, no significant differences in pCR rate, overall survival, or recurrence-free survival were observed between patients undergoing induction chemoradiation and induction chemotherapy. The reason for these results remained uncertain. For the radiation dose, as among the 30 patients undergoing surgical resection after induction therapy and achieving pCR, approximately one-third received only 30 Gy, the lower radiation dose did not appear to have such a great influence on these results. These results may be influenced by the relatively small number of patients included in this study.

The present study has several limitations. This was a single institutional study with nonrandomized retrospective features. In addition, a relatively small number of patients with pCR who underwent surgical resection after induction therapy were evaluated, and we could review only patients receiving induction therapy and surgical resections. Finally, although the median observation

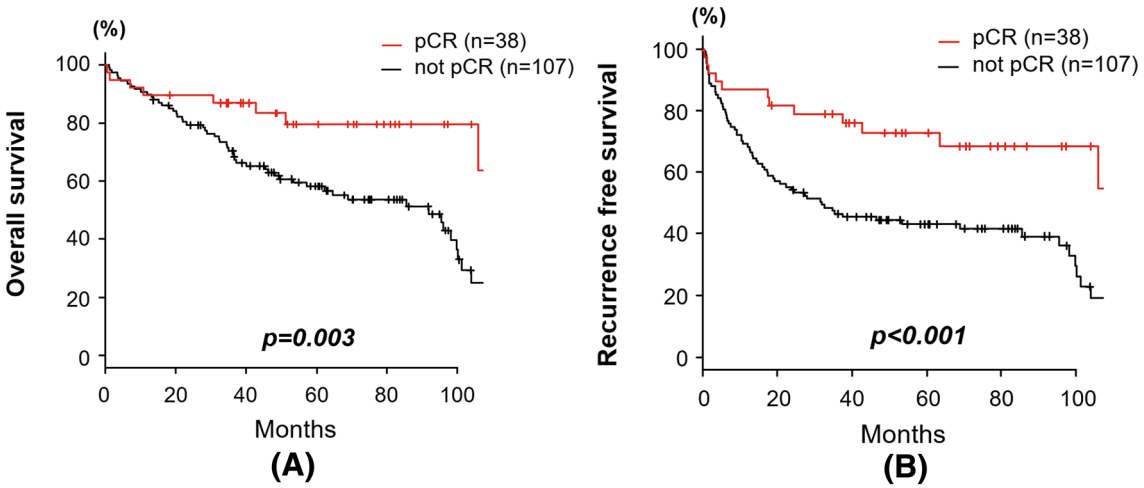

Fig. 1 **a** The overall survival of patients with NSCLC who achieved pCR was significantly better than that of patients who did not achieve pCR. The 5-year overall survival rate in all 38 cases of NSCLC with pCR was 79.5%. **b** The recurrence-free survival of patients with NSCLC who achieved pCR was significantly better than that of patients who did not achieve pCR. The 5-year recurrence-free survival rate in all 38 cases was 72.6%. *NSCLC* non-small cell lung cancer, *pCR* pathological complete response

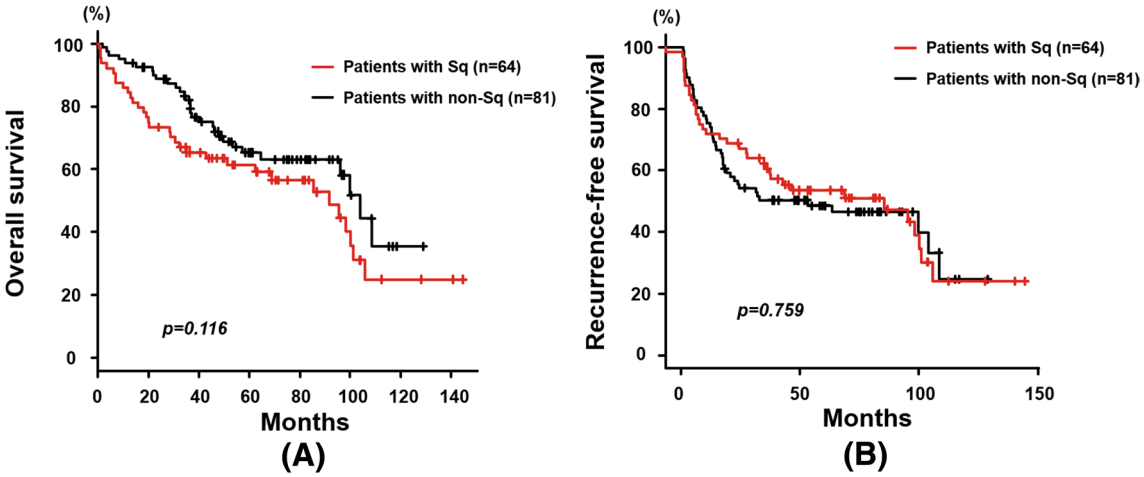

Fig. 2 **a** The overall survival of patients with NSCLC who underwent surgical resection after induction therapy was compared between patients with and without squamous cell carcinoma. There was no significant difference in overall survival. **b** In addition to overall survival, there was no significant difference in recurrence-free survival between patients with and without squamous cell carcinoma. *NSCLC* non-small cell lung cancer, *Sq* squamous cell carcinoma

period was longer than 4 years, to gain a more complete understanding of the prognosis of these patients, a longer observation period is required.

In conclusion, squamous cell carcinoma was found to be a positive predictive factor for achieving pCR. The prognosis of patients with NSCLC who had achieved pCR after undergoing surgical resection following induction therapy was excellent; however, a few cases of recurrence of NSCLC occurred, and the most frequent site of recurrence was the brain.

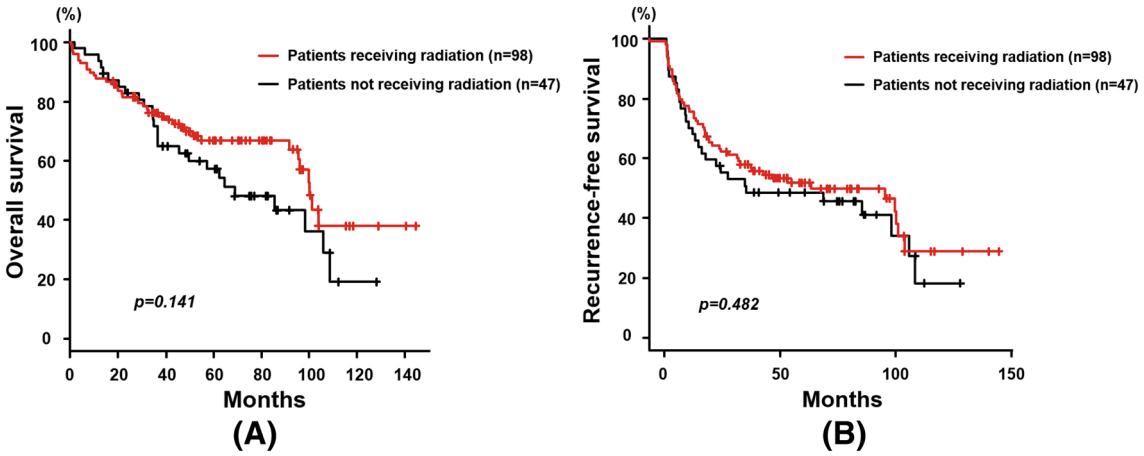

Fig. 3 **a** The overall survival of patients with NSCLC who underwent surgical resection after induction therapy was compared between patients that received and did not receive radiation therapy. There was no significant difference in overall survival. **b** Similarly, there was no significant difference in recurrence-free survival between patients that received radiation therapy and patients that did not receive radiation therapy. *NSCLC* non-small cell lung cancer

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Compliance with ethical standards

Conflict of interest None declared.

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