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ORIGINAL ARTICLE

# Clinical outcome of patients with recurrent non-small cell lung cancer after trimodality therapy

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## Abstract

**Purposes** The purpose of this study was to review the clinical course of patients with recurrence after induction chemoradiotherapy followed by surgery (trimodality therapy) for locally advanced non-small cell lung cancer (LA-NSCLC) and to identify the factors associated with favorable clinical outcome after recurrence.

**Methods** We analyzed the records of 140 patients with LA-NSCLC who were treated with trimodality therapy between 1999 and 2014.

**Results** Recurrence developed after trimodality therapy in 48 patients. A yp-N positive status was associated with a high risk of recurrence (HR, 2.05; $P=0.048$). Of the 45 of these patients able to be assessed retrospectively, 18 had oligometastatic recurrence and 20 underwent local treatment with curative intent. Local treatment was most frequently given to patients with oligometastatic recurrence ($P<0.001$). The median post-recurrence survival (PRS) was 41.4 months, and the 2-year PRS rate was 62%. Patients who received local treatment showed better PRS ($P=0.009$). The presence of liver metastasis ($P=0.008$), bone metastasis ($P=0.041$), or dissemination ($P<0.0001$) were associated with worse PRS.

**Conclusion** The survival of patients who received aggressive local treatment for postoperative recurrence after trimodality therapy for LA-NSCLC was better than that of patients who did not.

**Keywords** Lung cancer · Induction chemoradiotherapy · Oligometastasis · Oligorecurrence · Local treatment

## Introduction

Lung cancer is a prevalent disease with a high mortality rate. Although surgery is the best treatment option for patients with early-stage disease, most lung cancers are detected at an advanced stage; therefore, only 20–25% of tumors are suitable for surgical resection [1]. Trimodality therapy, consisting of induction chemoradiotherapy (CRT) followed by surgery, is a potential treatment option for patients with locally advanced (LA) non-small cell lung cancer (NSCLC), such as N2-3, bulky N1, or T3-4 stage disease with the invasion of structures including chest wall, carina, left atrium, superior vena cava, or pulmonary artery. Although this strategy is not widely accepted as a standard therapy, some recent reports suggest that it can achieve favorable outcomes in a subset of patients [2–6]. The outcomes of LA-NSCLC patients treated with trimodality therapy at Okayama University Hospital have been reported previously [4–8]. However, even after completing this intensive treatment, postoperative recurrence will develop in a subset of patients. Patients with distant metastatic recurrences are generally considered to have systemic disease, which is regarded as incurable. Oligometastasis is loosely defined as a limited number of metastatic lesions in a limited number of organs. Nevertheless, some patients have a relatively good prognosis following this treatment, even after postoperative recurrence. To our knowledge, the clinical course of patients with postoperative recurrence after trimodality therapy for LA-NSCLC has not been well documented and the prognostic factors of this population remain unclear. Thus, we reviewed the clinical

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outcomes of patients with recurrence after intensive trimodality therapy and sought to identify the prognostic factors.

## Materials and methods

### Patients

We perform trimodality therapy for NSCLC patients with mediastinal nodal metastasis. It is also used selectively for localized N3 or T3-4N0-1M0, but with large and invasive tumors, such as bulky N1, chest wall invasion, or T4 involvement, to achieve complete resection with a pathologic safety margin, based on the physician's discretion. Between January, 1999 and September, 2014, a total of 140 consecutive LA-NSCLC patients were treated with trimodality therapy at Okayama University Hospital. This study was approved by the institutional review board/ethical committee of Okayama University (Permission number: 1055). We used the tumor, node, metastasis classification system for NSCLC, 7th edition, proposed by the International Association of the Study of Lung Cancer, for disease staging [9].

### Treatment plan and follow-up after trimodality therapy

Details of trimodality therapy as the initial therapy targeting the primary tumor and associated outcomes have been described previously [4–6]. Briefly, most patients were given docetaxel and cisplatin as part of their induction chemotherapy, although ten patients received alternative chemotherapy regimens. Radiotherapy was started on the first day of chemotherapy, with a total radiation dose of 40–46 Gy planned. Dose escalation of radiotherapy up to 60 Gy was allowed for tumors that responded poorly. The surgical procedure after induction treatment was decided based on the disease extent prior to induction treatment. Lobectomy with complete ipsilateral mediastinal and subcarinal nodal dissection was the preferred approach; however, bilobectomy or pneumonectomy was performed to achieve complete resection, if required. Postoperative adjuvant treatment was administered at the physicians' discretion.

During the first 2 years after trimodality therapy for the primary tumor, patients were monitored closely every 3 months. These routine follow-ups included physical examination; blood tests, including for tumor markers; chest and abdominal computed tomography; 18-fluoro-2-deoxyglucose positron emission tomography scan; and enhanced brain MRI. From 3 to 5 years post-treatment, these examinations were performed every 6 months. After 5 years, blood tests and chest X-rays were performed annually, with further imaging only when deemed necessary. In this study, new recurrent lesions within 3 months from the diagnosis of initial postoperative recurrence were regarded as one of the initial recurrent lesions, to account for potential oversight of recurrence.

### Treatment plan and follow-up after postoperative recurrence

The treatment strategy for initial postoperative recurrence was planned by a team of oncologists, radiologists, and oncological surgeons. The feasibility of local treatment was calculated based on the location, number, size, and resectability of the metastatic lesions. Methods of local treatment included surgical resection, radiation therapy, or radiofrequency ablation (RFA), according to the following guidelines.

(1) *For brain metastases* Either surgical resection or radiation therapy, as stereotactic irradiation (STI) and whole brain radiotherapy (WBRT), at the discretion of the radiologist and neurosurgeon.
(2) *For adrenal gland metastases* Surgical resection.
(3) *For lung metastases* Surgical resection, STI, or RFA.
(4) *For lymph node metastases* Surgical resection or conventionally fractionated radiotherapy.

For the other patients, systemic chemotherapy, palliative radiation therapy, or best supportive care was chosen. Oligometastasis has been clinically defined as a limited number of metastatic lesions in a restricted number of organs. For the purpose of this study, oligometastasis was defined as 1–3 metastatic lesions in the brain, or an isolated extracranial metastatic lesion, for consistency with previous studies [10–13]. After local treatment was administered for recurrence, we used the same follow-up procedure as for trimodality therapy. Follow up of patients with systemic treatment was planned by the attending physicians based on the patient's condition.

### Statistical analysis

The risk of recurrence was calculated using competing risk methods, which account for deaths before recurrence as competing events. The cumulative incidence function was used to evaluate the cumulative incidence of recurrence (CIR) after trimodality therapy of the primary site. Differences were tested using the Gray method for univariate analyses or the Gray and Fine model for multivariate analyses.

For patients with recurrence, post-recurrence survival (PRS) was calculated from the date of the initial recurrence after the trimodality therapy for the primary site until the date of death or the most recent follow-up. Survival curves were generated using the Kaplan–Meier method and between-group differences were compared using the

log-rank test for univariate analyses. Data analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria) [14]. All statistical tests were two-sided and probability values of $<0.05$ were considered significant.

## Results

### Patient characteristics and risk factors for postoperative recurrence

Table 1 summarizes the clinical profiles of the 140 patients who underwent trimodality therapy for LA-NSCLC and the incidence of recurrence. Mediastinal lymph node metastasis was confirmed pathologically in 57 patients (40.7%), by mediastinoscopy or endobronchial ultrasound-guided transbronchial biopsy, prior to induction CRT. The median follow-up period after the beginning of CRT was 45.4 months (range 3.0–179 months), the median age was 61 years (range 31–78 years), and recurrence developed in 48 patients (34%). The 5-year CIR for all patients was 37.8% [95% confidence interval (CI), 28.9–46.6%; Fig. 1a]. Most recurrences were found within 2 years after the beginning of CRT; however, the recurrence rate remained elevated for the first 4 years after CRT. Univariate analysis revealed that pathological responses for the primary lesions ($P=0.005$) and the yp-N status ($P=0.001$) were significantly associated with recurrence (Table 1; Fig. 1b), and that pathological complete response (p-CR) for CRT tended to be related to a lower risk of recurrence; however, this was not significant ($P=0.055$). Factors with a $P$ value of less than 0.1 were used for multivariate analysis, and the yp-N-positive status was an independent predictive factor of a higher risk for recurrence (HR 2.05; 95% CI 1.01–4.17; $P=0.048$; Table 2).

### Characteristics of patients with postoperative recurrence and prognostic factors for post-recurrence survival

Next, we focused on the clinical outcomes of the 48 patients with recurrence after trimodality therapy. After the exclusion of three patients lost to follow-up, we assessed 45 patients retrospectively. The median follow-up period after initial recurrence was 40.6 months (range 0.9–161 months) and the median age was 58 years (range 32–77 years). Table 3 summarizes the characteristics of these 45 patients. Based on the criteria of oligometastasis, outlined in our Methods, 18 patients (40%) were in the oligometastatic recurrent disease group. The median recurrence-free interval, being the period between the administration of trimodality therapy for the primary tumor and initial recurrence, was 12.1 months (range 4.1–73.9 months). The lung was the most frequent location

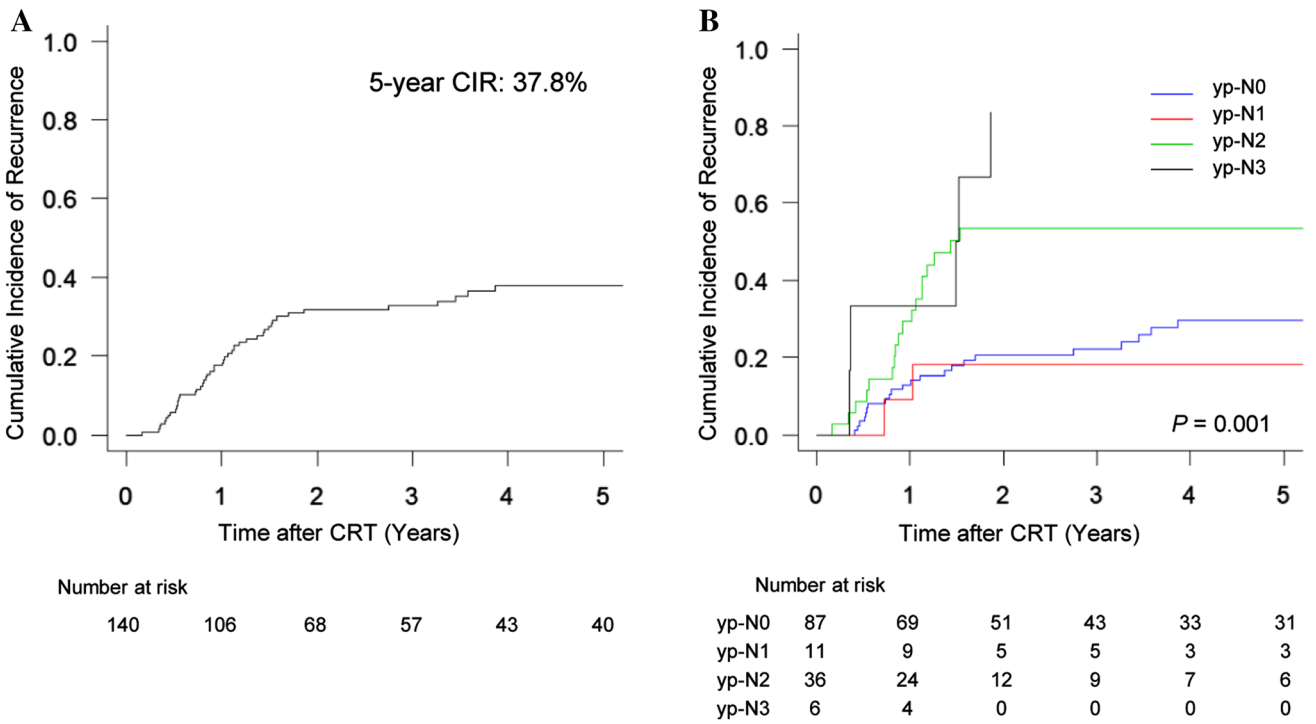


**Fig. 1** Cumulative incidence of recurrence (CIR). **a** Total CIR for patients with LA-NSCLC treated with trimodality therapy. **b** CIR for patients with LA-NSCLC who were treated with trimodality therapy based on py-N stage

**Table 1** Clinical characteristics and the incidence of recurrence ($n=140$)

| Characteristics | Number | 5-year CIR (95% CI), % | *P* value |
|---|---|---|---|
| All patients | 140 | 37.8 (28.9–46.6) | |
| Primary tumor related factor | | | |
| Age (years) | | | |
| <61 | 70 | 39.2 (27.0–51.3) | 0.84 |
| ≥61 | 70 | 36.3 (23.4–49.2) | |
| Sex | | | |
| Male | 108 | 35.7 (25.3–46.2) | 0.15 |
| Female | 32 | 50.8 (31.4–67.3) | |
| Smoking history | | | |
| Never | 22 | 56.5 (32.3–74.9) | 0.052 |
| Ever | 118 | 34.2 (24.7–43.9) | |
| Histological subtypes | | | |
| AD | 81 | 44.8 (32.2–56.7) | 0.12 |
| Non-AD | 59 | 28.2 (16.5–41.0) | |
| c-Stage | | | |
| IIA, T2bulkyN1 | 6 | 20.0 (20–20) | 0.42 |
| IIB, T3 (chest wall) N0 | 9 | 12.7 (12.7–12.7) | |
| IIIA | 81 | 41.8 (29.6–53.4) | |
| IIIB | 40 | 35.5 (21.0–50.3) | |
| IV | 4 | 50.0 (0.06–84.5) | |
| Trimodality therapy-related factor | | | |
| Induction chemotherapy | | | |
| CDDP + DOC | 130 | 37.1 (28.0–46.3) | 0.46 |
| Others | 10 | 46.7 (11.5–76.5) | |
| Induction radiation dose | | | |
| ≤46 Gy | 122 | 41.3 (31.3–51.0) | 0.053 |
| >46 Gy | 18 | 17.1 (3.9–38.1) | |
| Pulmonary resection | | | |
| Lobectomy[a] | 116 | 39.5 (29.5–49.4) | 0.81 |
| Bilobectomy | 15 | 28.1 (10.2–49.5) | |
| Pneumonectomy | 9 | 33.3 (6.7–64.0) | |
| Pathological response[b] | | | |
| 0 | 2 | 0 | 0.005 |
| 1 | 27 | 69.6 (44.5–85.0) | |
| 2 | 59 | 36.7 (23.2–50.3) | |
| 3 | 52 | 25.5 (13.8–39.0) | |
| yp-N | | | |
| 0 | 87 | 29.9 (19.5–41.1) | 0.001 |
| 1 | 11 | 18.2 (4.8–38.4) | |
| 2 | 36 | 53.5 (34.9–69.0) | |
| 3 | 6 | 83.3 (1.6–99.2) | |
| yp-CR | | | |
| Yes | 42 | 24.3 (11.6–39.5) | 0.055 |
| No | 98 | 43.6 (32.4–54.2) | |
| Adjuvant chemotherapy | | | |
| Yes | 56 | 44.9 (29.6–59.0) | 0.43 |
| No | 84 | 33.2 (22.5–44.3) | |

*CIR* Cumulative incidence of recurrence, *CI* confidence interval, *AD* adenocarcinoma, *CDDP* cisplatin, *DOC* docetaxel, *CR* complete response

[a]Lobectomy: lobectomy ($n=92$), sleeve lobectomy ($n=10$), lobectomy plus sub-lobar resection ($n=13$), or sublobar resection ($n=1$)

[b]The pathological response for primary lesion was categorized as follows: 0, no necrosis of tumor cells; 1, > 1/3 tumor cells viable; 2, < 1/3 tumor cells viable; 3, no viable tumor cells

**Table 2** Multivariate analysis of factors predicting postoperative recurrence

| Factor | HR | 95% CI | *P* value |
|---|---|---|---|
| Smoking history (never vs ever) | 1.41 | 0.70–2.85 | 0.33 |
| Induction radiation dose (≤46 Gy vs >46 Gy) | 2.24 | 0.68–7.38 | 0.19 |
| Pathological response[a] (0–2 vs 3) | 1.99 | 0.58–6.81 | 0.27 |
| yp-N (1–3 vs 0) | 2.05 | 1.01–4.17 | 0.048 |
| yp-CR (no vs yes) | 1.63 | 0.38–6.99 | 0.51 |

*HR* Hazard ration, *CI* confidence interval, *CR* complete response

[a]The pathological response for primary lesion was categorized as follows: 0, no necrosis of tumor cells; 1, > 1/3 tumor cells viable; 2, < 1/3 tumor cells viable; 3, no viable tumor cells

of recurrence (36%), followed by the brain (24%), lymph nodes (20%), and bone (20%). A solitary lung lesion developed in five patients, four of whom underwent CT-guided lung biopsy. All four tumors had the same histopathological findings as the original primary tumor, with no evidence of a separate primary tumor based on the pathologist's report, indicative of a metachronous metastatic recurrence. Twenty patients underwent local treatment with curative intent and the other 25 received systematic chemotherapy or palliative care. Table 4 summarizes the clinical profiles stratified by local treatment. Local treatment was performed more frequently in patients with oligometastasis ($P<0.0001$), those with brain metastases ($P=0.006$), and those with only brain metastases ($P=0.0006$). On the other hand, it was performed less frequently in those with bone metastases ($P=0.002$), and dissemination ($P=0.012$).

Over a median follow-up of 40.6 months, 26 deaths after initial postoperative recurrence were recorded. The median PRS time was 41.4 months after initial postoperative recurrence (95% CI 12.8–NA). The 2- and 5-year PRS rates were 62.4% and 36.5%, respectively (Fig. 2a). The 2-year PRS rates were 87.4% for patients who underwent local treatment and 44.6% for patients who did not ($P=0.009$; Fig. 2b). In this small cohort of patients, univariate analyses revealed that those with liver metastasis ($P=0.008$), bone metastasis ($P=0.041$), or disseminated recurrence ($P<0.0001$) and those who did not undergo local treatment ($P=0.009$) had worse PRS (Table 3).

## Details of local treatment for initial postoperative recurrence

We reviewed details about the 20 patients in the local treatment group (Table 5). Sixteen patients (80%) who had oligometastatic recurrences and four patients (patient nos 17, 18, 19, and 20) who had non-oligometastatic recurrent lesions underwent local treatment. Two of the patients with non-oligometastatic recurrent lesions had more than three brain metastases, another had three supraclavicular lymph node

**Table 3** Clinical characteristics and univariate analyses for post-recurrence survival ($n=45$)

| Characteristics | Number | 2-year PRS (95% CI) (%) | *P* value |
|---|---|---|---|
| All patients | 45 | 62.4 (45.4–75.5) | |
| Primary tumor-related factors | | | |
| Age (years) | | | |
| < 58 | 21 | 52.4 (29.7–70.9) | 0.41 |
| ≥ 58 | 24 | 71.7 (44.5–87.3) | |
| Sex | | | |
| Male | 30 | 51.2 (29.8–69.1) | 0.61 |
| Female | 15 | 80.0 (50.0–93.1) | |
| Smoking history | | | |
| Never | 12 | 83.3 (48.2–95.6) | 0.28 |
| Ever | 33 | 52.9 (32.4–69.7) | |
| Histological subtypes | | | |
| AD | 30 | 68.6 (48.3–82.3) | 0.65 |
| Non-AD | 15 | 42.4 (13.4–69.4) | |
| c-Stage | | | |
| IIA | 1 | | 0.68[a] |
| IIB | 1 | | |
| IIIA | 29 | 64.3 (43.6–79.1)[a] | |
| IIIB | 13 | 57.1 (24.9–79.8)[a] | |
| IV | 1 | | |
| Trimodality therapy-related factors | | | |
| Induction chemotherapy | | | |
| CDDP + DOC | 42 | 62.8 (45.1–76.1) | 0.85 |
| Others | 3 | 66.7 (5.4–94.5) | |
| Induction radiation dose | | | |
| ≤ 46 Gy | 42 | 60.0 (42.4–73.8) | 0.76 |
| > 46 Gy | 3 | 100 (NA–NA) | |
| Pulmonary resection | | | |
| Lobectomy[b] | 39 | 63.1 (44.9–76.8) | 0.93 |
| Bilobectomy | 4 | 75.0 (12.8–96.1) | |
| Pneumonectomy | 2 | 50 (0.6–91) | |
| Pathological response[c] | | | |
| 1 | 15 | 70.9 (39.5–88.1) | 0.92 |
| 2 | 18 | 49.6 (23.6–71.1) | |
| 3 | 12 | 71.3 (34.4–89.8) | |
| yp-N | | | |
| 0 | 20 | 57.3 (29.9–77.4) | 0.35 |
| 1 | 2 | NA | |
| 2 | 18 | 68.7 (40.1–85.7) | |
| 3 | 5 | 40 (5.2–75.3) | |
| yp-CR | | | |
| Yes | 9 | 71.4 (25.8–92.0) | 0.43 |
| No | 36 | 60.1 (41.1–74.7) | |
| Adjuvant chemotherapy | | | |
| Yes | 21 | 71.4 (47.2–86.0) | 0.61 |
| No | 24 | 51.6 (26.3–72.1) | |
| Recurrence-related factors | | | |
| Relapse-free interval[d] | | | |
| ≤ 1 year | 22 | 52.5 (27.8–72.2) | 0.66 |
| > 1 year | 23 | 70.9 (46.1–85.8) | |
| Oligometastasis | | | |
| Yes | 18 | 78.4 (46.4–92.6) | 0.18 |
| No | 27 | 53.1 (32.3–70.2) | |
| Metastatic location | | | |
| Locoregional only | 5 | 100 | 0.11 |
| Distant | 40 | 57.0 (38.8–71.7) | |
| Metastatic location | | | |
| Brain only | 8 | 85.7 (33.4–97.9) | 0.70 |
| Extracranial | 37 | 57.0 (38.1–72.1) | |
| Lymph node metastasis | | | |
| Present | 11 | 58.3 (23.0–82.1) | 0.94 |
| Absent | 34 | 63.7 (43.9–78.1) | |
| Brain metastasis | | | |
| Present | 11 | 90.0 (47.3–98.5) | 0.19 |
| Absent | 34 | 52.4 (32.7–68.8) | |
| Lung metastasis | | | |
| Present | 16 | 63.8 (33.2–83.3) | 0.76 |
| Absent | 29 | 61.4 (39.8–77.2) | |
| Liver metastasis | | | |
| Present | 2 | 0 (NA–NA) | 0.008 |
| Absent | 43 | 65.8 (48.2–78.6) | |
| Bone metastasis | | | |
| Present | 9 | 41.7 (10.9–70.8) | 0.041 |
| Absent | 36 | 68.1 (48.5–81.5) | |
| Adrenal gland metastasis | | | |
| Present | 6 | 50.0 (5.8–84.5) | 0.51 |
| Absent | 39 | 63.6 (45.5–77.1) | |
| Soft tissue metastasis | | | |
| Present | 4 | 75.0 (12.8–96.1) | 0.80 |
| Absent | 41 | 61.7 (43.8–75.4) | |
| Dissemination | | | |
| Present | 7 | 14.3 (0.7–46.5) | < 0.0001 |
| Absent | 38 | 72.5 (53.5–84.7) | |
| Local treatment | | | |
| Yes | 20 | 87.4 (57.7–96.8) | 0.009 |
| No | 25 | 44.6 (24.2–63.2) | |

*PRS* Post-recurrence survival, *CI* confidence interval, *AD* adenocarcinoma, *CDDP* cisplatin, *DOC* docetaxel, *CR* complete response

[a]Analysis of c-stage IIA, IIB, IIIA vs IIIB, IV

[b]Lobectomy; lobectomy ($n=92$), sleeve lobectomy ($n=10$), lobectomy plus sublobar resection ($n=13$), or sub-lobar resection ($n=1$)

[c]Pathological response for the primary lesion was categorized as follows: 0, no necrosis of tumor cells; 1, > 1/3 tumor cells viable; 2, < 1/3 tumor cells viable; 3, no viable tumor cells

[d]Period from the date of administration of induction chemoradiotherapy to the date of detection of recurrence

**Table 4** Correlation between local treatment and recurrence patterns

| | | | |
|---|---|---|---|
| Oligometastasis | | | |
| Non-oligometastasis | 4 | 23 | < 0.0001 |
| Oligometastasis | 16 | 2 | |
| Brain | 6 | 0 | |
| Lung | 4 | 1 | |
| Lymph nodes (regional) | 3 | 1 | |
| Adrenal gland | 3 | 0 | |
| Metastatic location | | | |
| Locoregional only | 4 | 1 | 0.16 |
| Distant | 16 | 24 | |
| Metastatic location | | | |
| Brain only | 8 | 0 | 0.0006 |
| Extracranial | 12 | 25 | |
| Lymph node metastasis | | | |
| Present | 4 | 7 | 0.73 |
| Absent | 16 | 18 | |
| Brain metastasis | | | |
| Present | 9 | 2 | 0.006 |
| Absent | 11 | 23 | |
| Lung metastasis | | | |
| Present | 4 | 12 | 0.066 |
| Absent | 16 | 13 | |
| Liver metastasis | | | |
| Present | 0 | 2 | 0.50 |
| Absent | 20 | 23 | |
| Bone metastasis | | | |
| Present | 0 | 9 | 0.002 |
| Absent | 20 | 16 | |
| Adrenal gland metastasis | | | |
| Present | 4 | 2 | 0.38 |
| Absent | 16 | 23 | |
| Soft tissue metastasis | | | |
| Present | 0 | 4 | 0.12 |
| Absent | 20 | 21 | |
| Dissemination | | | |
| Present | 0 | 7 | 0.012 |
| Absent | 20 | 18 | |

metastases in a single station, and one had a solitary brain metastasis and adrenal metastases. These lesions were considered to be potentially controllable by local treatments. Three patients (nos. 3, 15, and 20) (15%) achieved long-term survival without disease for more than 5 years. In particular, patient no 20 achieved long-term, disease-free survival for more than 12 years after local treatment for initial recurrences in the brain and adrenal gland, in addition to RFA treatment for lung metastasis 8 months later.

The efficacy of local treatment for patients with solitary recurrences outside the brain or adrenal gland is unclear. In this study, eight patients underwent local treatment for extracranial and extra-adrenal gland metastatic sites. Six of these eight patients were alive and two (nos. 3 and 5) were disease-free for more than 3.5 years (82.4 months and 44.6 months, respectively).

## Discussion

We assessed the clinical outcomes of patients who underwent trimodality therapy for LA-NSCLC, with particular focus on those with postoperative recurrences. We found that the yp-N positive status was independently associated with a high risk of recurrence after trimodality therapy. This study also showed that patients with recurrence detected as liver metastasis, bone metastasis, or disseminated recurrence, and those who did not undergo local treatment, had an unfavorable survival prognosis.

The effectiveness of induction CRT for LA-NSCLC has been reported by our group and others [2–6], and the downstaging of mediastinal lymph nodal metastasis after induction CRT is thought to be a favorable prognosis factor [5, 7]. Our current study confirmed that the 5-year CIR for all patients with LA-NSCLC after trimodality therapy was relatively low (37.8%) and that the yp-N positive status was an independent predictor for recurrence.

Although patients with metastatic recurrences are generally considered to have systemic disease, which is regarded as incurable, several studies have reported the possible effectiveness of aggressive local treatment in patients with NSCLC with limited metastatic lesions, particularly those with solitary recurrent lesions in the brain or adrenal gland [10–13, 15–21]. The rationale for this strategy is based on the concept of oligometastasis, which was first proposed by Hellman and Weichselbaum [21]. They described an intermediate state of metastases, referred to as the oligometastatic state, between a purely localized and widely metastatic cancer state. They hypothesized that local treatment may improve the survival outcomes of these patients because of the relatively smaller number and sites of metastases. In the current study, most patients with oligometastasis underwent local treatment, which was a significant predictor of improved PRS. Notably, three patients (nos. 3, 15, and 20) who received local treatment achieved long-term survival for more than 5 years, without the evidence of recurrence, indicating that they were potentially cured.

Despite the lack of substantive evidence of efficacy, aggressive local treatment is used for only a selected subset of patients with oligometastatic recurrence. The National Comprehensive Cancer Network guidelines (ver.3.2016) recommend local treatment for both the brain and adrenal gland. These include surgical resection followed by WBRT,

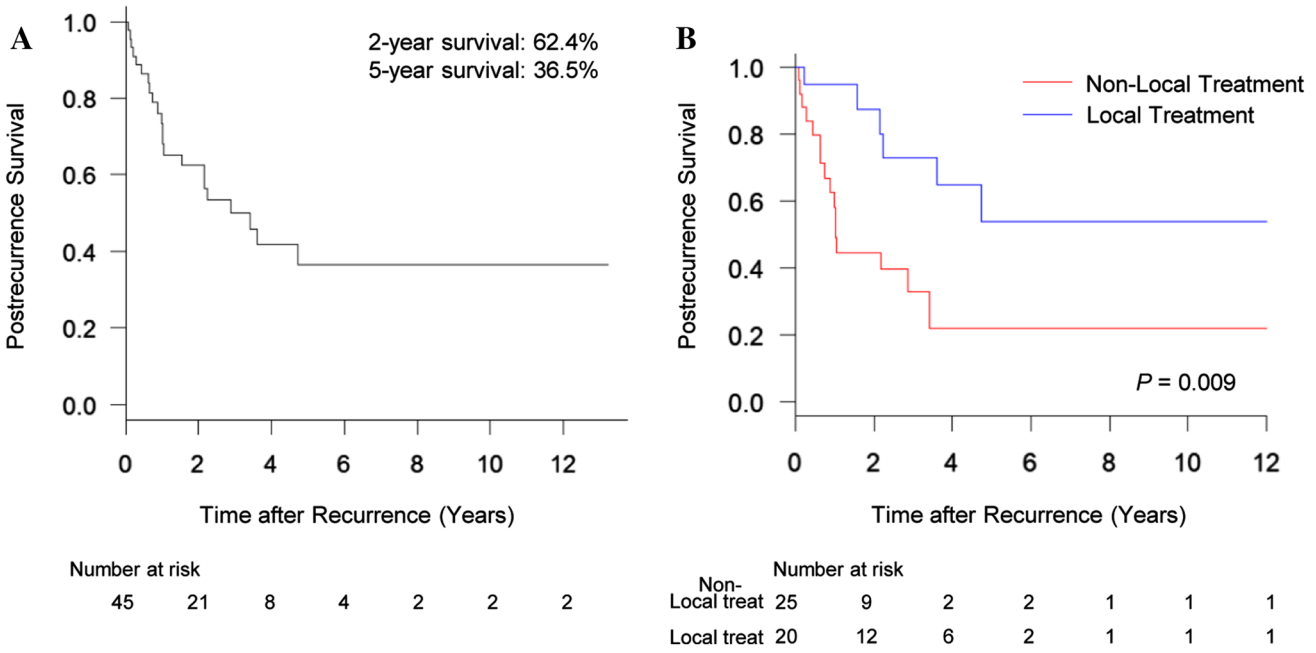


**Fig. 2** Postrecurrence survival. **a** Total postrecurrence survival of patients after initial recurrence. **b** Postrecurrence survival after initial recurrence based on the utilization of local treatment

SRS, or SRS + WBRT for the brain (recommendation category1 or 2A) and adrenalectomy or radiation therapy for the adrenal gland (category2B). The reported 5-year survival rates of patients managed with local treatment for isolated brain or adrenal gland metastatic lesions are 10–20% [17, 18] or 25–35% [16, 19], respectively.

The selection of patients who are likely to benefit from local treatment is of paramount importance because new recurrent lesions will be found soon after this treatment in a large proportion of patients with oligometastases. Several retrospective reports have suggested the key selection criteria as being a controlled primary tumor, the absence of nodal metastases (stage I or II NSCLC), and an oligometastatic state [10, 16, 20]. We identified that liver metastasis, bone metastasis, or disseminated recurrence were predictors of poor survival prognosis after initial postoperative recurrence, taking into account the small sample size studied, and that all those patients had other metastatic lesions, regarded as non-oligometastatic, and thus did not undergo local treatment. Contrary to our expectations, PRS was not influenced by factors related to the primary tumor or the trimodality therapy, including c-stage, pathological response status of the primary tumor for CRT, or yp-N status.

The benefit of local treatment for patients with solitary recurrences in sites other than the brain or adrenal gland is unclear. A systematic review found that local treatments might be as effective against other solitary metastases as they are against isolated brain or adrenal gland metastases [22]. In the present study, eight patients underwent local treatment for extracranial and extra-adrenal gland metastatic sites, resulting in long-term survival without disease in two (nos. 3 and 5). This suggests that aggressive local treatment for extracranial and extra-adrenal gland metastatic sites should be considered, despite the small sample size.

The present study has several limitations including its retrospective design, small sample size, considerable heterogeneity in the patient population, and bias in treatment selection. However, large-scale prospective studies are difficult to conduct owing to the rarity of patients with NSCLC with oligometastases and the heterogeneity of relapse patterns between patients. Therefore, we performed a retrospective analysis. In summary, local treatment can provide a chance of cure for selected patients because systemic therapy alone is unlikely to achieve complete remission.

## Conclusions

In conclusion, the survival of patients who underwent aggressive local treatment for postoperative recurrence after trimodality therapy for LA-NSCLC was better than that of patients who did not. Further studies are required to delineate the populations who would be most likely to benefit from aggressive local treatment.

**Table 5** Summary of local treatment group patient data

| Patient no. | Age | Sex | Histology | Primary treatment | | RFI[a] (months) | Recurrence | | | Outcome | Post-recurrence survival (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | c-stage | yp-N | | Site[b] (number) | Oligo-metastasis | Local treatment modality | | |
| 1 | 77 | M | SQ | IIIA | 0 | 16.5 | Lung (1) | Yes | Surg | Alive[c] | 4.7 |
| 2 | 67 | M | SQ | IIIA | 2 | 17.2 | Lung (1) | Yes | STI | Alive | 7.8 |
| 3 | 51 | M | AD | IIIB | 0 | 41.4 | Lung (1) | Yes | RFA | Alive[c] | 82.4 |
| 4 | 65 | M | SQ | IIIA | 0 | 9.6 | Lung (1) | Yes | RFA | Dead[d] | 9.1 |
| 5 | 65 | M | AD | IIIA | 0 | 12.1 | LN (1) | Yes | Surg | Alive[c] | 44.6 |
| 6 | 72 | M | ADSQ | IIIB | 0 | 73.9 | LN (1) | Yes | Surg | Dead | 43.9 |
| 7 | 51 | F | SQ | IIIA | 0 | 13.3 | LN (1) | Yes | cf-RT | Alive | 68.8 |
| 8 | 69 | M | AD | IIIA | 0 | 8.8 | Brain (3) | Yes | STI | Alive[c] | 0.9 |
| 9 | 58 | F | AD | IIIB | 0 | 17.3 | Brain (3) | Yes | STI + WBRT | Dead | 57.6 |
| 10 | 63 | F | AD | IIIA | 2 | 13.6 | Brain (2) | Yes | STI | Dead | 26.2 |
| 11 | 58 | M | AD | IIIA | 0 | 42.9 | Brain (1) | Yes | Surg | Alive | 64.8 |
| 12 | 57 | M | AD | IIIB | 0 | 6.3 | Brain (1) | Yes | Surg | Dead | 2.5 |
| 13 | 76 | F | AD | IIIA | 2 | 10.1 | Brain (1) | Yes | STI | Dead | 27.1 |
| 14 | 61 | M | SQ | IIIA | 2 | 6.7 | Adr (1) | Yes | Surg | Dead | 19.0 |
| 15 | 51 | M | AD | IIIA | 1 | 8.7 | Adr (1) | Yes | Surg | Dead[cd] | 67.5 |
| 16 | 58 | M | AD | IIIB | 0 | 9.3 | Adr (1) | Yes | Surg | Dead[d] | 9.3 |
| 17 | 68 | M | SQ | IIIA | 2 | 10.0 | Brain (5) | No | STI | Alive | 41.4 |
| 18 | 63 | M | AD | IIIA | 2 | 6.4 | Brain (7) | No | STI | Alive | 46.8 |
| 19 | 45 | F | AD | IIIA | 2 | 10.6 | LN (3) | No | cf-RT | Alive | 14.0 |
| 20 | 55 | F | SQ | IIIA | 0 | 4.9 | Brain (1), Adr (1) | No | STI, Surg | Alive[c] | 148.5 |

*RFI* Relapse free interval, *AD* adenocarcinoma, *SQ* squamous cell carcinoma, *Adr* adrenal gland, *LN* lymph node, *Surg* surgical resection, *STI* stereotactic irradiation, *WBRT* whole brain radiotherapy, *cf-RT* conventionally fractionated radiotherapy, *RFA* radiofrequency ablation

[a]The period between the date of administration of induction chemoradiotherapy and the date of initial recurrence

[b]Initial recurrent site

[c]Disease free

[d]Death from other disease

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## Compliance with ethical standards

**Conflict of interest** S. Toyooka had honorarium and grants and endowments from Taiho Pharmaceutical Co., Ltd. K. Kiura had honorarium, grants and endowments from Taiho Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., Ono Pharmaceutical Co., Ltd, and Nippon Boehringer Ingelheim Co., Ltd. No other authors have any conflicts of interest to declare.

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