



# The long-term prognosis of induction chemotherapy followed by surgery for N2 non-small cell lung cancer: A retrospective case series study



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## HIGHLIGHTS

- The long-term prognosis of induction chemotherapy followed by surgery for N2 NSCLC remains controversial.
- The median follow-up period was 7.89 years. The median DFI was 13.9 months. The 5-year OS was 56.9%.
- Our survival data were much better than those of past reports.

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## ABSTRACT

**Introduction:** The long-term prognosis of induction chemotherapy followed by surgery for N2 non-small lung cell cancer (NSCLC) remains controversial.

**Patients and methods:** We retrospectively reviewed the data and assessed the prognosis of 31 N2-NSCLC patients who underwent induction chemotherapy followed by surgery at our institution between January 1999 and December 2013. Potential prognostic factors, such as age, gender, tumor histology, tumor marker levels, tumor size, the number of N2 lymph nodes, the time from the last induction chemotherapy to the date of surgery, induction chemotherapy, RECIST response, downstaging status, pathological stage, adjuvant chemotherapy, and EF, were analyzed.

**Results:** The chemotherapy regimens of 30 of the 31 patients included a platinum agent. Complete resection was performed in 96.7% of the cases. Pathological downstaging was induced in 9 (29%) of the 31 patients. The median follow-up period was 7.89 years. The median DFI was 13.9 months. The recurrence rate was 74.2%. The 5-year OS was 56.9%. Univariate analyses revealed that none of the factors significantly affected OS, while the tumor histology had a significant effect on the DFI.

**Conclusion:** Although the recurrence rate in our study was similar to previous studies, our survival data were much better than those of past reports. Although the tumor histology was the only factor that had a significant association with DFI in the current study, the possibility of bias exists.

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## 1. Introduction

The therapeutic strategy for stage IIIA non-small cell lung cancer (NSCLC) with ipsilateral mediastinal nodal metastasis (N2) are the subject of ongoing debate. Surgery alone has been associated with a

poor outcome in some studies [1,2]. Induction chemotherapy followed by surgical resection has found general acceptance. Induction chemotherapy is performed to reduce the risk of micrometastatic progression and improve the resectability of NSCLC [3]. However, the long-term prognosis of induction chemotherapy followed by surgery for N2 NSCLC remains unclear. The aim of this retrospective study was to analyze the long-term prognosis of N2 NSCLC patients who undergo induction chemotherapy followed by surgery and to identify the prognostic factors, based on PROCESS Guidelines [4].

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## 2. Patients and methods

We retrospectively reviewed the records of 31 N2-NSCLC patients who underwent induction chemotherapy followed by surgery at National Hospital Organization, Okinawa National Hospital between January 1999 and December 2013. Twenty-nine of the patients with biopsy-confirmed N2 disease. N2 disease was clinically confirmed based on a CT scan ( $n = 2$ ), a CT scan combined with positron emission tomography (PET) ( $n = 10$ ), or a CT scan combined with Gallium scan ( $n = 19$ ).

The objective tumor response was evaluated using CT. A complete response (CR) was defined as 100% regression of the tumor, and a partial response (PR) was defined, according to the Response Evaluation Criteria in Solid Tumors (RECIST guideline version 1.1), as tumor regression of  $>30\%$ .

The pathological effect of induction chemotherapy was classified according to the General Rule for Clinical and Pathological Record of Lung Cancer, sixth edition [5] as a pathologically complete response (complete cancer cell death; Ef 3), a major response (fewer than one third of cancer cells were viable; Ef 2) or a minor response (more than one third of cancer cells were viable; Ef 1).

Overall survival (OS) was calculated from the date of the surgery and analyzed using the Kaplan-Meier method and the log-rank test. A multivariate analysis was performed using a Cox regression model. P values of  $<0.05$  were considered to indicate statistical significance. All of the data were analyzed using the JMP software, program (version 12, SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1. Patient characteristics

The study population included 24 males and 7 females, with a median age of 66 years (range, 46–78 years). All of the patients had a performance status (PS) score (Eastern Cooperative Oncology Group [ECOG]) of 0 or 1. The tumors included 15 adenocarcinomas, 14 squamous cell carcinomas (Sq), and 2 adenosquamous carcinomas. Their characteristics are shown in Table 1.

### 3.2. Clinical response

Sixteen patients received cisplatin plus docetaxel, 12 received carboplatin plus paclitaxel, 1 received gemcitabine plus vinorelbine, 1 received cisplatin plus docetaxel and cisplatin plus gemcitabine, and 1 received cisplatin plus gemcitabine. The median numbers of courses of induction chemotherapy was 2 (range, 1–5). The clinical response to the induction chemotherapy was CR in 1 patient, PR in 18, SD in 11 patients, and PD in 1 patient. Concerning the clinical stage (yc), downstaging was induced in 7 (22.6%) of the 31 patients.

### 3.3. Surgery

The median time from the induction chemotherapy until surgery was 35 days (range, 21–68 days). The mean operative time was 384 min (range, 214–794 min), and the mean blood loss was 465 ml (range, 50–1732 ml). The surgical procedures included lobectomy ( $n = 25$ ), bilobectomy ( $n = 3$ ), lobectomy with bronchial plasty ( $n = 1$ ), and lobectomy with pulmonary arterial plasty ( $n = 2$ ). There were no cases of operative mortality. Complete tumor resection with microscopically negative margins was achieved in 30 cases. The resection was incomplete in one patient due to the presence of microscopic residual cancer cells in the parietal pleura. Complete resection was performed in 96.8% of the patients. The morbidity and 30-day mortality rates were 9.35 and 0%,

respectively. The morbidity included prolonged air leakage in 2 patients and bronchial stamp fistula in 1 patient.

### 3.4. Pathological response

With regard to the pathological effects of induction chemotherapy, 4 (12.9%) patients had an Ef 3 response, 3 (9.6%) had an Ef 2 response and 24 (77.4%) had an Ef 1 response. With regard to the pathological stage (yp), downstaging was induced in 9 (29%) of the 31 patients. The pathological stage (yp) of 22 patients (70.7%) corresponded with the clinical stage (yc), while the pathological stage of 4 patients was worse than the clinical stage.

### 3.5. Prognosis and recurrence

The median follow-up period was 7.89 years. The median disease-free interval (DFI) was 13.9 months. The global 5-year overall survival rate (OS) was 58.7% (Fig. A); the 5-year OS rates in the non-SQ and SQ patients were 49.3% and 70.7% respectively ( $p = 0.983$ ) (Fig. B), while the 5-year OS rates in the patients with an Ef 1, Ef 2 and Ef 3 response were 61.3, 66.6, and 37.5%, respectively ( $p = 0.238$ ) (Fig. C). The 5-year OS rates in the patients with and without pathological downstaging were 85.7 and 52.4%, respectively ( $p = 0.696$ ) (Fig. D). The recurrence rate was 74.2%. The univariate analysis of the clinical and pathological characteristics associated DFI and OS are shown in Table 2. Although none of the factors were significantly associated with OS, a significant association was found between the tumor histology and DFI on (Sq, 23.5 months; Non-Sq, 6.7 months;  $p = 0.041$ ). At the final follow-up examination, 4 patients were alive and free of cancer and 5 patients were alive with cancer. Eighteen patients died of cancer and 4 patients died of other causes (second primary lung cancer [ $n = 2$ ], interstitial pneumonitis [ $n = 1$ ], and unknown cause [ $n = 1$ ]).

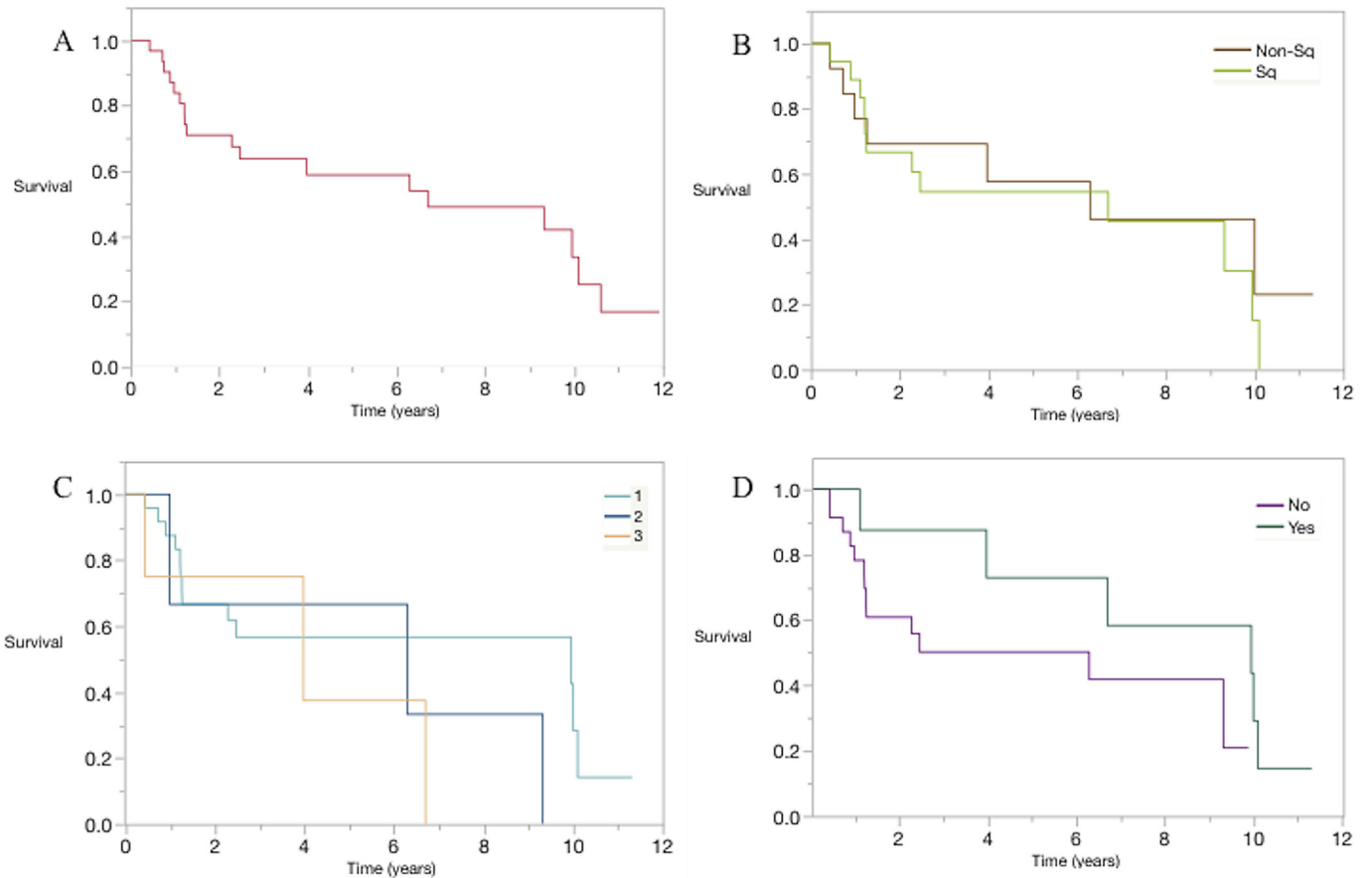
## 4. Discussion

This study evaluated the long-term outcomes of induction chemotherapy followed by surgery in patients with N2 NSCLC. Induction chemotherapy was initiated during the 1980s. Since then, several meta-analyses have reported that induction chemotherapy significantly improves survival in comparison to surgery alone [6–9]. Furthermore, several factors have been previously reported to predict a favorable long-term outcome in patients who are treated with a multimodal approach, including the clinical and pathological response to chemotherapy, the ability to completely resect the tumor and the mediastinal lymph nodes, and the complete clearance of N2 disease [3,10–12]. In the current study, patients with squamous cell carcinoma had a significantly higher DFI than patients with adenocarcinoma. To the best of our knowledge, other previous studies involving induction chemotherapy failed to find such an association. In general, the degree of differentiation, and lymphatic and blood vessel invasion are generally related to the risk of recurrence. However, the current study could not find an association because it was impossible to precisely evaluate cancer tissue that was damaged by induction chemotherapy. Thus, there may be some bias in the results related to the histologic subtype, and to lymphatic and blood vessel invasion. A greater accumulation of such patients or a prospective trial is needed to identify the prognostic value of the histological subtype.

Most previous studies have involved short- to medium-term follow-up periods, while those that have investigated the long-term outcomes have lacked statistical power [13–18]. On the other hand, some studies with long- to medium-term follow-up periods demonstrated 5-year OS rates of 35–43% in patients with N2 NSCLC who received induction chemotherapy [3,12,19]. Our

**Table 1**  
Patient characteristics.

Characteristics	No. of patients
Gender	
Male/Female	24/7
Age, years, median(range)	64 (46–78)
Smoking status	
Never/Former/Current	2/10/19
Tumor histology	
Sq/Non-Sq	14/17
N2 status assessment method	
CT/Biopsy/CT&PET-CT/CT& Gallium scan	2/2/8/19
The number of N2 lymph nodes	
Single/Multiple	12/19
Tumor size,mm, median (range)	42 (12–1000)
Serum tumor marker	
Increase/Decrease	22/9
The number of times of Induction chemotherapy, median (range)	2 (1–5)
Induction chemotherapy	
Cisplatin + Docetaxel/Carboplatine + Paclitaxel/Others	16/12/3
Clinical stage following chemotherapy	
IA/IB/IIA/IIIB/IIIA	3/2/1/1/24
RECIST response	
CR/PR/SD/PD	1/19/10/1
Time from last induction chemotherapy to date of surgery, median days, range	35 (21–68)
Pathological stage following chemotherapy	
0/IA/IB/IIA/IIIB/IIIA	1/1/3/1/0/25
Adjuvant chemotherapy	
Yes (Cisplatin + Docetaxel/Carboplatine + Paclitaxel/Others)/No	20 (5/12/3)/11
Ef	
1/2/3	24/3/4



**Fig.** (A) The global 5-year overall survival rate. (B) The 5-year OS rates in the non-Sq and Sq patients. (C) The 5-year OS rates in the patients with an Ef 1, Ef 2 and Ef 3 response. (D) The 5-year OS rates in the patients with and without pathological downstaging.

**Table 2**

The univariate analysis of the clinical and pathological characteristics associated DFI (disease-free interval) and OS (overall survival).

Parameter	Median DFI (months)	Log-Rank <i>P</i> value	MST <sup>a</sup> (years)	Log-Rank <i>P</i> value
Gender		0.398		0.487
Male	15.5		9.9	
Female	6.7		6.3	
Age, years		0.928		0.592
≥64 years	19.8		6.3	
<64 years	12.8		9.3	
Tumor histology		<b>0.041</b>		0.983
Sq	23.5		9.3	
Non-Sq	6.7		3.9	
Tumor marker		0.288		0.574
Increase	12.0		6.7	
Decrease	30.3		9.3	
Tumor size		0.179		0.503
≥42 mm	24.9		9.9	
<42 mm	12.2		6.3	
The number of N2 lymph node		0.284		0.186
Single	9.0		2.4	
Multiple	25.0		9.3	
Time from last induction chemotherapy to date of surgery		0.792		0.319
≥36 days	13.0		6.7	
<36 days	13.8		6.3	
Induction chemotherapy		0.311		0.311
Cisplatin + Docetaxel	22.5		9.3	
Carboplatin + Paclitaxel	12.2		6.3	
Others	6.9		6.7	
RECIST response		0.397		0.293
CR or PR	25.0		9.3	
SD	11.2		6.7	
PD	10.9		1.2	
Pathological downstaging		0.282		0.404
Yes	36.6		9.9	
No	11.3		6.3	
Pathological stage		0.492		0.531
0 or I	36.6		10.1	
II	75.7		6.96	
III	11.2		6.3	
Adjuvant chemotherapy		0.971		0.365
Yes	12.6		9.9	
No	9.0		2.3	
Ef		0.360		0.238
1	12.9		9.9	
2	6.7		6.3	
3	19.8		3.9	

<sup>a</sup> MST: median survival time.

survival data were much better. However, the median DFI and the recurrence rate in the present study were 13.9 months and 74.2%, respectively. This was similar to the results of previous studies [3,12,19]. This means that treatments for recurrence, such as chemotherapy or radiation therapy, contributed to improving the long-term prognosis of the patients in the current study. In recent years there has been remarkable progress in chemotherapy for recurrent NSCLC, including driver mutation and molecular-targeted therapy. We hypothesize that this progress will continue to improve the prognosis of patients with recurrent NSCLC. Furthermore, progress in relation to the development of induction chemotherapeutic drugs may improve curability.

Although the various incidences of postoperative morbidity and mortality after induction chemotherapy have been reported in previous studies [14,15,18], the frequency of morbidity was low and there were no cases of perioperative mortality in our series.

Although the efficacy of induction chemoradiation therapy in N2 NSCLC has recently been established [20–22], one study failed to find a survival benefit in comparison to induction chemotherapy [23]. A greater accumulation of such patients or a prospective trial is needed to identify the efficacy of concurrent chemoradiation therapy in comparison to induction chemotherapy for N2 NSCLC.

The present study is associated with some limitations. First, this

was a single center, retrospective study. Second, the sample size was small. Third, with the exception of 2 patients, all of the patients were diagnosed with N2 based on imaging findings; however, the N2 mediastinal lymph nodes were affected by induction chemotherapy in all of the patients. Therefore, although the potential risk is low, it is possible the incidence of N2 was overestimated. Despite these limitations, our survival data were much better than those of past reports. However, prospective randomized trials are needed to verify the long-term outcomes of induction chemotherapy followed by surgery for N2 NSCLC.

In conclusion, although the chance that induction chemotherapy followed by surgery will achieve a permanent cure in patients with N2 NSCLC is not high, the use of this multimodal treatment in patients with recurrent disease achieves a greater improvement in the long-term prognosis than conventional therapy.

#### Ethical approval

This study is retrospectively viewed.

#### Sources of funding

Naohiro Taira and the other co-authors have no relevant

financial interests to declare in this manuscript.

### Author contribution

Naohiro Taira: writing the paper, Hidenori Kawasaki: study concept.

Tomonori Furugen: data collection, Takaharu Ichi: data collection.

Kazuaki Kushi: data collection, Tomofumi Yohena: study design.

Tsutomu Kawabata: study design.

### Conflict of interest statement

Naohiro Taira and the other co-authors have no conflicts of interest and relevant financial interests to declare in this manuscript.

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Naohiro Taira, Hidenori Kawasaki.

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