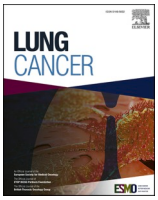
Lung Cancer 199 (2025) 108027

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan



Real-world status of multimodal treatment of Stage IIIA-N2 non-small cell lung cancer in Japan: Results from the SOLUTION study, a non-interventional, multicenter cohort study

Hidehito Horinouchi [a], Haruyasu Murakami [b], Hideyuki Harada [c], Tomotaka Sobue [d], Tomohiro Kato [e], Shinji Atagi [f], Toshiyuki Kozuki [g], Takaaki Tokito [h], Satoshi Oizumi [i], Masahiro Seike [j], Kadoaki Ohashi [k], Tadashi Mio [l], Takashi Sone [m], Chikako Iwao [n], Takeshi Iwane [n], Ryo Koto [n], Masahiro Tsuboi [o,*]

[a] Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan
[b] Department of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan
[c] Division of Radiation Therapy, Shizuoka Cancer Center, Shizuoka, Japan
[d] Division of Environmental Medicine and Population Sciences, Graduate School of Medicine, Osaka University, Osaka, Japan
[e] Department of Respiratory Medicine, National Hospital Organization Himeji Medical Center, Hyogo, Japan
[f] Department of Thoracic Oncology, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan
[g] Department of Thoracic Oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Ehime, Japan
[h] Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University Hospital, Fukuoka, Japan
[i] Department of Respiratory Medicine, National Hospital Organization Hokkaido Cancer Center, Hokkaido, Japan
[j] Department of Pulmonary Medicine and Oncology, Nippon Medical School Hospital, Tokyo, Japan
[k] Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan
[l] Department of Respiratory Medicine, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
[m] Department of Respiratory Medicine, Kanazawa University Hospital, Ishikawa, Japan
[n] Department of Medical, AstraZeneca K.K., Osaka, Japan
[o] Department of Thoracic Surgery, National Cancer Center Hospital East, Chiba, Japan

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Surgery
Adjuvant therapy
Neoadjuvant therapy
Chemoradiotherapy
Observational study
Retrospective study

ABSTRACT

Objectives: There is limited consensus on resectability criteria for Stage IIIA-N2 non-small cell lung cancer (NSCLC). We examined the patient characteristics, N2 status, treatment decisions, and clinical outcomes according to the treatment modality for Stage IIIA-N2 NSCLC in Japan.

Materials and methods: Patients with Stage IIIA-N2 NSCLC in Japan were consecutively registered in the SOLUTION study between 2013 and 2014. Patients were divided according to treatment (chemoradiotherapy [CRT], surgery + perioperative therapy [neoadjuvant and/or adjuvant therapy], surgery alone). Demographic characteristics, N2 status (number and morphological features), pathological information, and treatments were analyzed descriptively. Overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS) were estimated using the Kaplan–Meier method.

Results: Of 227 patients registered, 133 underwent CRT, 56 underwent surgery + perioperative therapy, and 38 underwent surgery alone. The physicians reported the following reasons for unresectability for 116 of 133 CRT patients: large number of metastatic lymph nodes (70.7 %), extranodal infiltration (25.0 %), poor surgical tolerance (19.0 %), or other reasons (18.1 %). CRT was more frequently performed in patients whose lymph nodes had an infiltrative appearance (64.3 %) and was the predominant treatment in patients with multiple involved stations (discrete: 60.0 %; infiltrative: 80.4 %). Distant metastasis with/without local progression was found in 50.4 %, 50.0 %, and 36.8 % of patients in the CRT, surgery + perioperative therapy, and surgery alone groups, respectively. The respective 3-year OS and DFS/PFS rates (median values) were as follows: surgery +

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; DFS, disease-free survival; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; RT, radiotherapy.

* Corresponding author at: Department of Thoracic Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa-shi, Chiba 277-8577, Japan.
E-mail address: mtsuboi@east.ncc.go.jp (M. Tsuboi).

https://doi.org/10.1016/j.lungcan.2024.108027
Received 29 March 2024; Received in revised form 24 October 2024; Accepted 11 November 2024
Available online 14 November 2024

perioperative therapy—61.9 % (not reached) and 37.1 % (22.4 months; DFS); CRT group—42.2 % (31.9 months) and 26.8 % (12.0 months; PFS); surgery alone group—37.7 % (26.5 months) and 28.7 % (12.6 months; DFS). *Conclusion:* This study has illuminated the real-world decision rules for choosing between surgical and non-surgical approaches in patients with Stage IIIA-N2 NSCLC. Our landmark data could support treatment decision making for using immune checkpoint inhibitors and targeted therapy for driver oncogenes in the perioperative therapy era.

1. Introduction

Stage IIIA-N2 non-small cell lung cancer (NSCLC) is a highly heterogenous cancer with broad patient and disease characteristics in terms of the number and status of lymph node metastases [1,2]. For many years, radical surgery was the mainstay treatment approach if deemed feasible. In the last decade, it has become clear that patients with Stage IIIA-N2 NSCLC should be considered for multimodal therapies, including chemotherapy (CT), radiotherapy (RT), or chemoradiotherapy (CRT), which may be performed alone or in combination with surgery [3–14]. The treatment selection process should take into account the presence/extent of mediastinal lymph node metastasis, for which surgical and non-surgical treatments may be considered.

Although the decision-making process for determining treatment of Stage IIIA-N2 NSCLC is influenced by the results of phase 3 trials, there is some controversial evidence regarding the superiority of surgery after induction therapy versus curative CRT [15–17]. Consequently, the criteria for selecting either surgery or CRT as curative treatment remain unclear, resulting in considerable variation in the selected treatments for Stage IIIA-N2 NSCLC [18] and a complicated decision-making process.

This clinical situation is at least partly due to the significant heterogeneity of patients with Stage IIIA-N2 NSCLC, which includes pN2 preoperatively, cN2 with imaging diagnosis, occult N2 diagnosed preoperatively as cN0/1 but histologically diagnosed as pN2 postoperatively, bulky N2, single cN2, and multiple cN2. The inconsistent criteria for determining resectability may also contribute to the differing results among the earlier phase 3 trials and cohort studies.

In recent years, immune checkpoint inhibitors have advanced the treatment of Stage III NSCLC. CRT followed by durvalumab improved overall survival (OS) and other outcomes in patients with unresectable Stage III NSCLC in phase 3 trials [19,20]. After the approval of durvalumab in the United States, Japan, and other countries, CRT followed by durvalumab has become a standard of care for unresectable Stage III NSCLC, and its effectiveness has been demonstrated in real-world clinical practice [21]. Immune checkpoint inhibitors are also promising for perioperative treatment of Stage IIIA-N2 NSCLC. Atezolizumab after adjuvant CT improved disease-free survival (DFS) in patients with Stage II–IIIA NSCLC [22]. Furthermore, the addition of nivolumab to neoadjuvant CT delayed recurrence in patients with Stage IB–IIIA NSCLC [23]. Thus, immune checkpoint inhibitors may become a useful option for the treatment of both unresectable and resectable Stage IIIA-N2 NSCLC. In order to guide the treatment decision-making process in clinical practice in the future immunotherapy era, it will be important to clarify the background characteristics and treatment outcomes of patients with Stage IIIA-N2 NSCLC who are treated in real-world settings.

To address this knowledge gap, we analyzed data from the SOLUTION study [24] to obtain insight into the clinical decisions surrounding the resectability and treatment choice for this cohort in clinical settings. In particular, we examined the patient characteristics, treatment decisions, and clinical outcomes of patients treated in a real-world setting in Japan according to their treatment modality (CRT or surgery ± perioperative therapy).

2. Methods

2.1. Ethics

The design of the non-interventional SOLUTION study is described in more detail in the prior reports [24,25]. As previously explained, this study adhered to the Ethical Guidelines for Medical and Health Research Involving Human Subjects [26], which incorporate the ethical principles of the Declaration of Helsinki. The study was registered on the University hospital Medical Information Network database (UMIN000031385). Eleven institutions participated in this study under approval from their ethics committees. Between March 2019 and September 2019, the study investigators obtained informed consent from surviving patients; patients who had died or moved from the participating site could be registered if the patient or legal representative had an opportunity to provide consent by opt-out.

2.2. Study design and patient selection

Briefly, patients aged ≥20 years were eligible for this study if they were diagnosed with Stage III NSCLC between January 2013 and December 2014 and underwent surgery, CRT, CT, or RT, providing consent was obtained [24]. Patients who received palliative care as their sole treatment or an unapproved drug, or who had a primary cancer other than NSCLC were excluded. The medical records of eligible patients were reviewed through to the index date (March 1, 2018) to extract clinical information including background characteristics, treatment modality, and outcomes. NSCLC was staged according to the 7th version of the American Joint Committee on Cancer Staging Manual [27]. For the purpose of this study, we focused on patients with Stage IIIA-N2 NSCLC who underwent either CRT or surgery ± perioperative therapy (Fig. S1). All data were collected retrospectively, and all treatment decisions were made by the clinical care teams. To avoid selection bias at patient enrollment, all eligible patients were consecutively registered in each institution. There were no limitations on the numbers of patients registered at each participating institution.

2.3. Endpoints and data analyses

The following data were used in this analysis: baseline characteristics, treatments, reasons for not performing surgery, definition of death (within 30 or 90 days after surgery), disease characteristics, and clinical outcomes (OS, progression-free survival [PFS] for patients who underwent CRT, and DFS for patients who underwent surgery ± perioperative therapy). PFS included local or distant progression. DFS was defined as the time from surgery to disease recurrence in patients who underwent R0 resection. These data were analyzed in patients who underwent CRT, surgery + perioperative therapy, and surgery alone. The surgery + perioperative and surgery alone groups were also combined as a surgery ± perioperative therapy group. Subgroup analyses were also performed according to the appearance and number of lymph node metastases (appearance: discrete or infiltrative; number: single or multiple station). The Kaplan–Meier method was used to plot the OS, PFS, and DFS curves, and to estimate the median survival times and the survival rates at 1–5

years with 95 % confidence intervals (CIs). Other data were analyzed using descriptive statistics, which included the number (percent) of patients and median (range) as appropriate. All analyses were conducted in an exploratory manner and no formal between-group comparisons were made. Missing values were not replaced/imputed. SAS® System Release 9.2 or higher (SAS Inc., Cary, NC, USA) was used for the data analyses.

3. Results

3.1. Patient disposition

Among 744 patients with Stage III NSCLC registered in the SOLUTION study, 227 were classified as Stage IIIA-N2 and were included in the present analyses (Fig. S1). Of these, 133 underwent CRT (CRT group), 56 underwent surgery + perioperative therapy, and 38 underwent surgery alone. Thus, the surgery ± perioperative therapy group comprised 94 patients. For the CRT and surgery ± perioperative groups, the median (range) follow-up times were 30.9 (1.9–61.8) and 33. 5

Table 1
Patient characteristics.

Characteristic	CRT N = 133		Surgery + perioperative therapy N = 56		Surgery alone N = 38		Surgery ± perioperative therapy N = 94	
Age								
Median (range), years	65.0	(41–85)	62.5	(34–78)	69.0	(49–84)	67.0	(34–84)
≥65 years	72	(54.1)	24	(42.9)	28	(73.7)	52	(55.3)
Sex								
Male	104	(78.2)	48	(85.7)	31	(81.6)	79	(84.0)
Female	29	(21.8)	8	(14.3)	7	(18.4)	15	(16.0)
Smoking history								
Current smoker	34	(25.6)	28	(50.0)	13	(34.2)	41	(43.6)
Past smoker	86	(64.7)	23	(41.1)	22	(57.9)	45	(47.9)
Non-smoker	13	(9.8)	5	(8.9)	3	(7.9)	8	(8.5)
ECOG PS								
0	87	(65.4)	45	(80.4)	30	(78.9)	75	(79.8)
1	43	(32.3)	9	(16.1)	6	(15.8)	15	(16.0)
2	2	(1.5)	1	(1.8)	1	(2.6)	2	(2.1)
Missing data	1	(0.8)	1	(1.8)	1	(2.6)	2	(2.1)
Comorbidities	95	(71.4)	46	(82.1)	33	(86.8)	79	(84.0)
COPD	21	(15.8)	15	(26.8)	8	(21.1)	23	(24.5)
Autoimmune disease	5	(3.8)	3	(5.4)	2	(5.3)	5	(5.3)
ILD	1	(0.8)	3	(5.4)	6	(15.8)	9	(9.6)
IPF	0		2	(3.6)	3	(7.9)	5	(5.3)
Non-IPF	0		0		3	(7.9)	3	(3.2)
Unknown	1	(0.8)	1	(1.8)	0		1	(1.1)
Other	83	(62.4)	41	(73.2)	24	(63.2)	65	(69.1)
T classification								
T1a	19	(14.3)	7	(12.5)	3	(7.9)	10	(10.6)
T1b	23	(17.3)	14	(25.0)	5	(13.2)	19	(20.2)
T2a	40	(30.1)	24	(42.9)	11	(28.9)	35	(37.2)
T2b	23	(17.3)	4	(7.1)	7	(18.4)	11	(11.7)
T3	26	(19.5)	7	(12.5)	12	(31.6)	19	(20.2)
T4	0		0		0		0	
Tx	2	(1.5)	0		0		0	
Histological type								
Adenocarcinoma	66	(49.6)	34	(60.7)	18	(47.4)	52	(55.3)
Squamous cell carcinoma	52	(39.1)	16	(28.6)	16	(42.1)	32	(34.0)
Neuroendocrine tumor (NSCLC)	6	(4.5)	2	(3.6)	1	(2.6)	3	(3.2)
Other	9	(6.8)	4	(7.1)	3	(7.9)	7	(7.4)
Primary lesion location[a]								
Right upper lobe	54	(40.6)	26	(46.4)	16	(42.1)	42	(44.7)
Right middle lobe	4	(3.0)	5	(8.9)	1	(2.6)	6	(6.4)
Right lower lobe	34	(25.6)	8	(14.3)	12	(31.6)	20	(21.3)
Left upper lobe	22	(16.5)	14	(25.0)	5	(13.2)	19	(20.2)
Left lower lobe	19	(14.3)	4	(7.1)	4	(10.5)	8	(8.5)
Unknown	2	(1.5)	0		0		0	

Values are n (%) of patients, unless stated otherwise.
COPD, chronic obstructive pulmonary disease; CRT, chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSCLC, non-small cell lung cancer.
[a] Patients may be included in multiple categories.

(0.6–61.7) months, respectively.

3.2. Characteristics of patients with Stage IIIA-N2 NSCLC

The background characteristics of the patients are summarized in Table 1. Of note, the median age was numerically similar in the CRT and surgery ± perioperative therapy groups (65.0 and 67.0 years, respectively), although the proportion of elderly patients (≥65 years) was numerically greater in patients who underwent surgery alone than those who underwent surgery + perioperative therapy (73.7 % and 42.9 %, respectively). Some differences in other background characteristics between the CRT group and the surgery ± perioperative therapy group are also apparent, including a higher proportion of patients with a performance status (PS) of 1 (32.3 % and 16.0 %, respectively) and lower proportion of patients with comorbidities (71.4 % and 84.0 %, respectively) in the CRT group. As might be expected, patients with a history of interstitial lung disease predominantly underwent surgery alone (15.8 %).

3.3. Physicians' reasons for determining unresectability

Surgery was not performed in 133 patients; these patients underwent CRT instead. Of these, 116 were classified as unresectable. As illustrated in Fig. 1, the three major reasons reported by the physician for not performing surgery in individual patients (multiple reasons may apply) were a large number of metastatic lymph nodes (70.7 %), extranodal infiltration (25.0 %), and poor surgical tolerance (19.0 %). Seventeen patients were considered resectable but did not undergo surgery for various reasons (Fig. 1).

3.4. Overview of surgical and non-surgical treatments

The treatment modalities are summarized in Tables S1 (surgical procedures), S2 (use of neoadjuvant or adjuvant therapies in the surgery + perioperative therapy group), and S3 (RT procedures in the CRT group). Lymph node dissection was performed in 78.7 % of patients (Table S1), primarily ND2a-2 (lymph node resection up to groups 1a, 1b, 2a-1, and 2a-2) according to the Japanese classification [28]. Resection was considered complete with no residual tumor in 79.8 % of patients; this value was lower in those who underwent surgery alone than in those who underwent surgery + perioperative therapy (73.7 % and 83.9 %, respectively).

Two patients (one in the surgery alone group and one in the surgery + perioperative therapy group) did not undergo surgery but they were included in the relevant groups because surgery was planned (Table S1). Among 56 patients who underwent surgery + perioperative therapies, 11 received neoadjuvant and adjuvant therapies, 15 received neoadjuvant therapies, and 30 received adjuvant therapies (Table S2). Regarding RT procedures, nearly all underwent X-ray radiation therapy (98.5 %) targeted at the affected sites (Table S3). Most patients received a total dose of ≥54 to ≤66 Gy (88.0 %). The lung volume irradiated with ≥20 Gy per the treatment plan (V20) was ≥25 % in 50.4 % of patients, and the mean lung dose (MLD) was ≥13 Gy in 51.9 %.

3.5. Lymph node status

The baseline characteristics of patients divided by number (single or multiple station) and appearance (discrete or infiltrative) of lymph node metastases and treatment modality are summarized in Fig. 2 and Tables S4 and S5. In patients with lymphadenopathy in a single station, surgery + perioperative therapy was the most frequent procedure in those with a discrete appearance (41.1 %) whereas CRT was the most frequent procedure in those with an infiltrative appearance (64.3 %) (Fig. S2, Table S6). By comparison, among patients with lymphadenopathies in multiple stations, CRT was the predominant modality regardless of whether the appearance was discrete (60.0 %) or infiltrative (80.4 %).

3.6. Distant metastasis

Regarding post-treatment disease progression, local progression only was relatively infrequent in patients who underwent surgery +

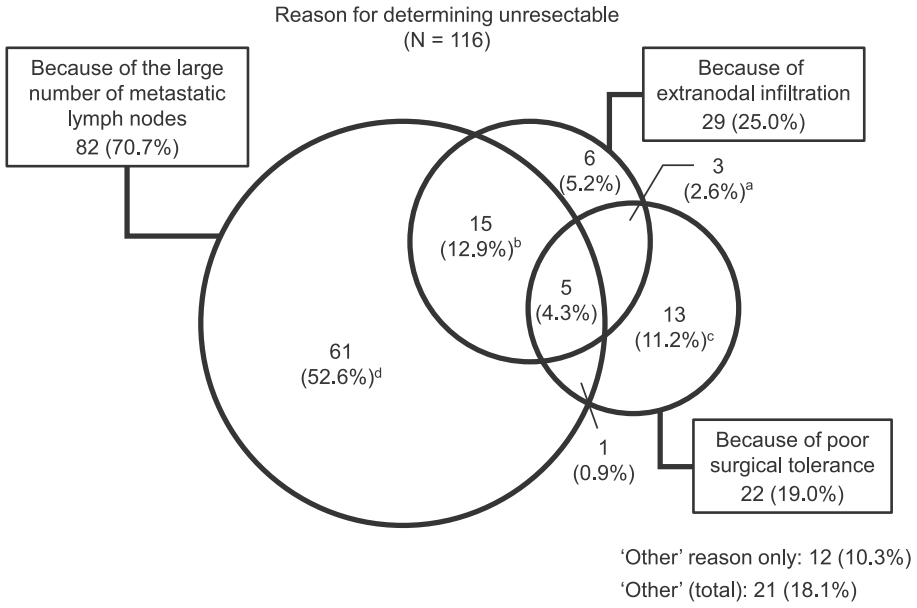


Fig. 1. Reasons for determining unresectability, as reported by the doctors for individual patients. Seventeen patients who received chemoradiotherapy (CRT) were considered to have resectable disease but did not undergo surgery due to the patient's preference (n = 8), the institution's policy (n = 4), because the patient had bulky N2 cancer, CRT was prioritized, and the possibility of surgery was to be reconsidered after treatment (n = 1), complicated pneumothorax (n = 1), the left lower lobe cancer was resectable and CRT was administered to the right upper lobe cancer before surgery (n = 1), difficulty in performing surgery first (n = 1), or comorbidities (n = 1). [a]Includes 1 patient (0.9 %) with other reasons. [b]Includes 1 patient (0.9 %) with other reasons. [c]Includes 4 patients (3.4 %) with other reasons. [d]Includes 3 patients (2.6 %) with other reasons.

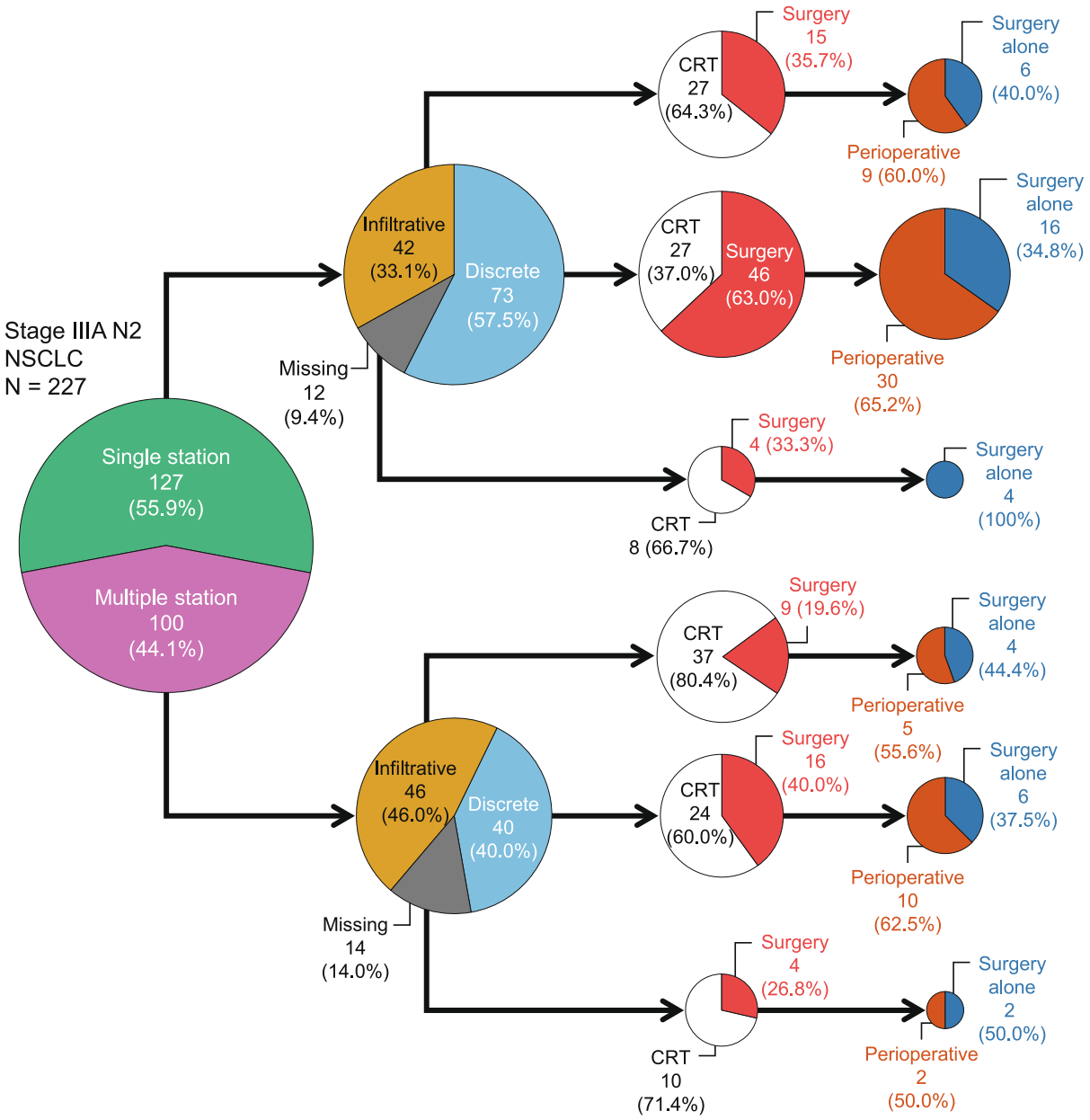


Fig. 2. Distribution of treatment strategies. CRT, chemoradiotherapy; NSCLC, non-small cell lung cancer.

perioperative therapy (7.1 %), indicating relatively better local control. Local progression only was detected in 13.2 % of patients in the surgery alone group and 17.3 % of patients in the CRT group. Distant metastasis without local progression was found in similar percentages of patients who underwent surgery + perioperative therapy (30.4 %) or CRT (31.6 %) (Table S7).

3.7. OS, PFS, and DFS according to treatment modality and lymph node status

The Kaplan–Meier curves of OS and PFS/DFS in the CRT, surgery + perioperative therapy, and surgery alone groups are shown in Fig. 3. The survival curves for OS and DFS were numerically more favorable in the surgery + perioperative therapy group, with 3-year OS and DFS rates of 61.9 % and 37.1 %, respectively. The median OS and DFS were not reached and 22.4 months, respectively. In the CRT group, the median OS and PFS were 31.9 months and 12.0 months, and the 3-year OS and PFS rates were 42.2 % and 26.8 %, respectively. The corresponding values in the surgery alone group were 37.7 % (26.5 months) and 28.7 % (12.6 months).

When patients were subdivided according to the number of involved stations (single or multiple), there were apparent differences in OS and PFS/DFS between the single and multiple station subgroups of patients who underwent CRT (more favorable in patients with a single involved station) (Fig. 4a), but not in patients who underwent surgery alone (Fig. 4b) nor those who underwent surgery + perioperative therapy (Fig. 4c). The 3-year OS and PFS/DFS rates tended to be numerically more favorable in patients who underwent surgery + perioperative therapy and who had multiple involved stations compared with the other subgroups.

Survival outcomes were also assessed in patients divided by treatment and lymph node appearance (discrete or infiltrative), and the results are presented in Fig. S3. In patients who underwent CRT, the OS and PFS results did not tend to differ between those with discrete or infiltrative lymph node invasion (Fig. S3a). For patients who underwent surgery alone, DFS tended to be more favorable in those with discrete

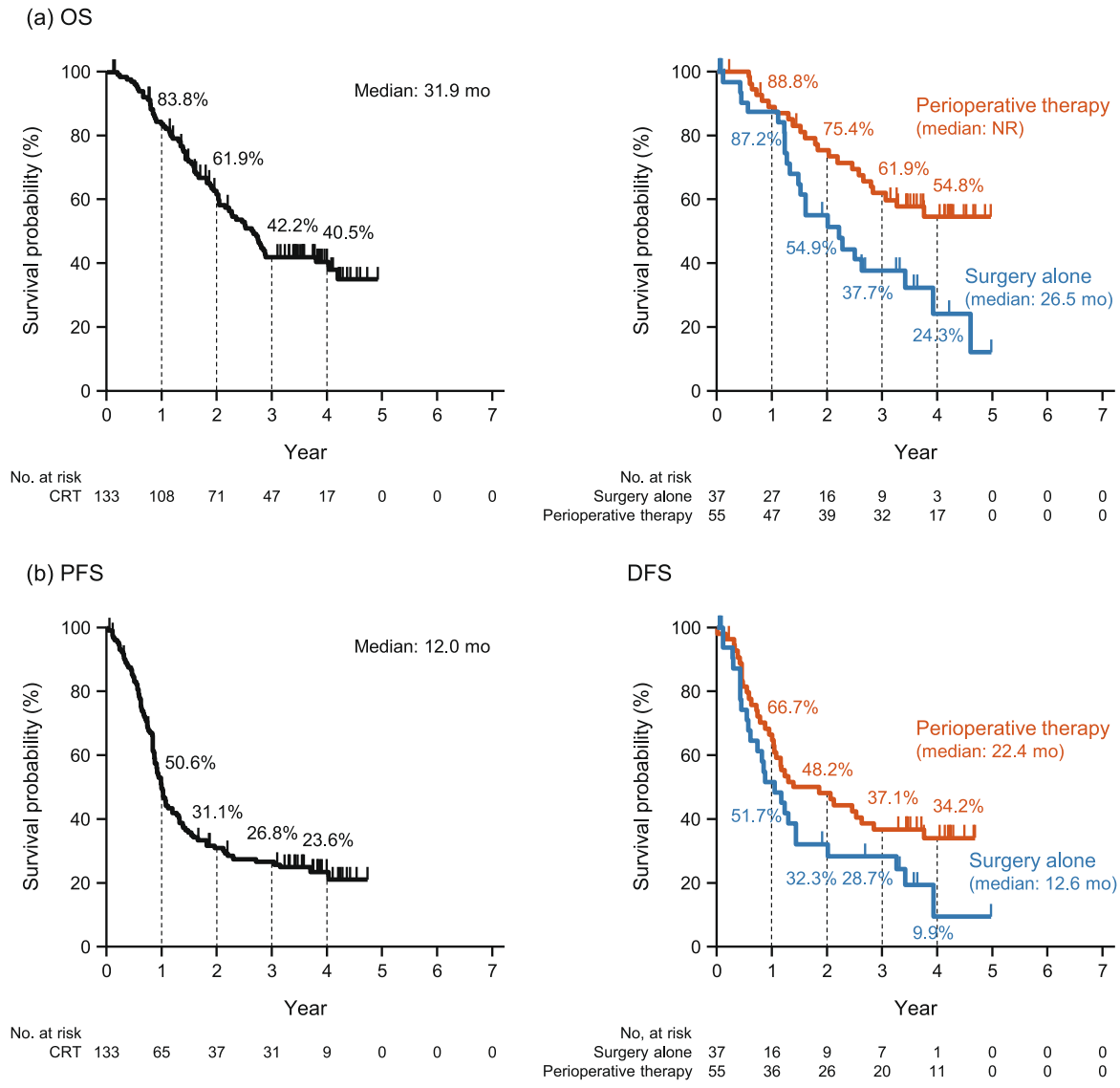


Fig. 3. OS (a) and PFS/DFS (b) according to the treatment modality in patients with Stage IIIA-N2 NSCLC. Left, CRT; right, surgery alone or surgery + perioperative therapy. Median (range) follow-up: CRT, 30.9 (1.9–61.8) months; surgery ± perioperative therapy, 33.5 (0.6–61.7) months. CRT, chemoradiotherapy; DFS, disease-free survival; mo, months; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

lymph node invasion (Fig. S3b). In patients who underwent surgery + perioperative therapy, OS, but not DFS, was numerically more favorable in those with infiltrative lymph node invasion than in those with discrete lymph node invasion (Fig. S3c). The 3-year survival rates tended to be more favorable in patients who underwent surgery + perioperative therapy than in the other groups. In this group, the 3-year OS rates for patients with infiltrative lymph node invasion and discrete lymph node invasion were 76.9 % and 60.0 %, respectively, and the 3-year DFS rates were 31.0 % and 41.0 %, respectively.

3.8. Death within 30 or 90 days after surgery

No death was identified up to 30 days after surgery. There was one confirmed death within 90 days after surgery in the surgery alone (2.6 %) group.

4. Discussion

This was the first multicenter observational study to report the relationship between treatment choice and detailed features of N2 status in patients with Stage IIIA NSCLC. This study has illuminated the reality of treatment decisions being made in clinical practice for this patient population, for which there is no clear consensus on the optimal treatment and where clinical practice differs between institutions and between physicians. The factors that had the greatest influence on the physicians' decisions on whether or not to perform surgery were the number and appearance of metastatic lymph nodes, which was also reflected in the percentages of times each treatment modality was selected. These findings are expected to be valuable for guiding treatment selection for patients with Stage IIIA-N2 NSCLC because this setting is expected to become more complex with the emergence of novel therapies in the future.

Resectability and unresectability were used as key eligibility criteria in earlier clinical studies of lung cancer. In previous reports, patients with resectable NSCLC were the logical target of studies that investigated the appropriate surgical procedure for patients with resectable Stage IA–II NSCLC [29–31]. In contrast, patients with unresectable NSCLC were enrolled in studies that investigated the optimal timing of RT or which CT regimen to combine with RT in patients receiving CRT, for example [20,32–35]. In those studies, the decision about whether the

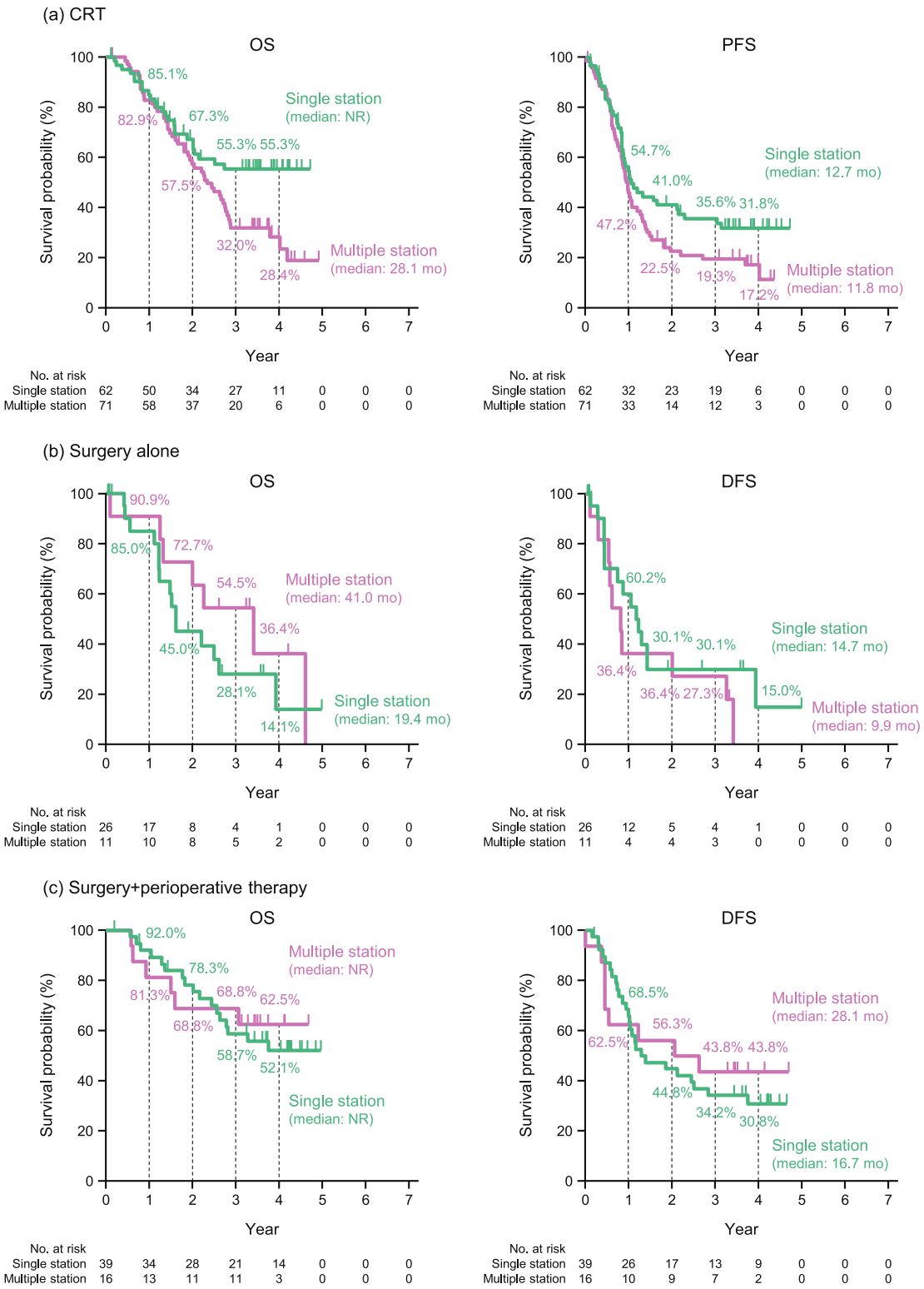


Fig. 4. OS (left) and PFS/DFS (right) according to the treatment modality (CRT [a], surgery alone [b], or surgery + perioperative therapy [c]) and number of lymph node metastases (single or multiple station). CRT, chemoradiotherapy; DFS, disease-free survival; mo, months; NR, not reached; OS, overall survival; PFS, progression-free survival.

tumor was resectable or not was essentially made by a multidisciplinary team or often by the surgeons alone, but consensus regarding resectability/unresectability was not documented. Several studies have investigated the surgical indications for patients with NSCLC, including those with N2 disease, which is often discussed as borderline resectable/unresectable, and the impact of lymph node status on clinical outcomes [36,37]. In a French study of the treatment of Stage IIIA-N2 NSCLC, consensus was reached via multidisciplinary decision-making [38], but the patients were limited to those with a non-bulky/non-infiltrative lymph node appearance. Thus, the optimal management of Stage IIIA-N2 NSCLC patients, which is a very diverse population in terms of lymph node number and appearance, remains to be elucidated. In

addition, according to the latest Pan-Asian adapted European Society for Medical Oncology Clinical Practice Guidelines for NSCLC, lymph node status, swelling, and widespread mediastinal N2 infiltration should be considered when selecting the treatment strategy [39]. The Japanese guidelines strongly recommend that a multidisciplinary clinical team should be involved in making decisions about the treatment strategy for patients with Stage IIIA NSCLC [40], but do not provide specific selection criteria. In our investigation into the reasons for determining whether Stage IIIA-N2 NSCLC patients were resectable or unresectable in a real-world setting, we revealed that this decision encompassed multiple factors. We found three main reasons for unresectability: the number of metastatic lymph nodes, the extent of lymph node infiltration, and surgical tolerance. A large number of metastatic lymph nodes and extranodal infiltration were key reasons for determining unresectability. To explain this, patients with a large number of metastatic lymph nodes are more likely to have distant micrometastases that are difficult or impossible to detect using imaging, and therefore have a high risk of postoperative distant metastasis, even in the early stages of NSCLC [41–43]. Additionally, the number of metastatic lymph nodes is strongly associated with the prognosis of NSCLC [44–46]. Another reason why clinicians may use lymph node metastasis/infiltration as a criterion for determining resectability relates to the possibility of extranodal extension, which is associated with poor prognosis of NSCLC [47–49]. These factors related to determining resectability are based on information that is provided by many different departments (e.g., surgery, internal medicine, and pathology), and our findings in real-world clinical practice support the recommendations in the guidelines. Additionally, we suggest that appropriate subanalyses, eligibility criteria, and allocation adjustment factors, based on the number of metastatic lymph nodes and appearance, are needed when designing future clinical studies that include patients with Stage IIIA-N2 NSCLC for whom it is difficult to determine a treatment modality, especially in studies in the perioperative period using immuno-oncology agents.

Our study has also clarified the clinical realities of the treatment modalities of patients who are considered to be resectable. It should be noted that the surgery alone group had a numerically higher median age and a greater proportion of patients with a PS of 0 than the other treatment modalities, but this group did not receive neoadjuvant/adjuvant therapies, even though the PS suggested that many patients were medically fit for such therapies. That group also tended to be older than the surgery + perioperative group, and perioperative therapy may not be considered feasible due to the risk of CT-related adverse events [50,51] or comorbidities, such as chronic kidney disease, that contraindicate certain CT regimens. In patients who received perioperative therapy, the treatment modalities varied.

Studies of lung cancer treatment in the perioperative era [22,23,52–55] have yielded a rapidly growing body of preoperative and postoperative evidence regarding the treatment modalities for Stage IIIA-N2 NSCLC. As such, there is an increasing number of treatment options, including immune checkpoint inhibitors, but the criteria for determining the resectability and selecting the treatment modality for patients with Stage IIIA-N2 NSCLC are still controversial and vary among studies [56]. Thus, we believe that the management of patients with Stage IIIA-N2 NSCLC in real-world clinical practice will become even more complicated in the future, and clinicians will need to consider which treatment modality (surgery, CRT ± immune checkpoint inhibitor) is most appropriate for patients with infiltrative lymph node invasion, multiple lymph node metastasis, or low surgical tolerance. In real-world settings, the determination of resectability differs between patients and the therapies are chosen accordingly. Further evidence is needed to support such treatment decisions, including the possibility of altering the treatment based on the clinical course (e.g. response to neoadjuvant therapy), as well as pathological findings (e.g. number of metastatic lymph nodes, infiltrative lymph node invasion), and patient factors (e.g. surgical tolerance).

The proposed revisions for the forthcoming 9th Edition of the TNM Classification of Lung Cancer have separated N2 into single station (N2a) and multiple station (N2b), with distinct survival outcomes and prognoses [57]. Those findings are consistent with the results of our study regarding the number of lymph node metastases. Our findings provided further insight into the clinical value of lymph node metastasis-related factors, such as lymph node appearance, that are also considered in treatment decisions.

Our findings should be interpreted with caution due to the limitations. This study was a retrospective observational study. All patients who satisfied the eligibility criteria were enrolled consecutively in the order in which they were diagnosed in order to prevent selection bias in patient enrollment. It should be noted that analysis of survival time was based on the selected modality, and these data could not be directly compared due to the limited number of patients and the heterogeneity of patient characteristics for each modality.

In conclusion, this study has illuminated the real-world decision rules for choosing between surgical and non-surgical approaches in patients with Stage IIIA-N2 NSCLC. Our landmark data could support treatment decision making for using immune checkpoint inhibitors and targeted therapy for driver oncogenes in the perioperative therapy era.

Study registration

University hospital Medical Information Network database (UMIN000031385).

Prior publication

Selected data from this manuscript were presented as abstracts/posters at the 61st Annual Meeting of the Japan Lung Cancer Society (2020) and the 37th Annual Meeting of the Japanese Association for Chest Surgery (2020).

Related articles

H. Murakami, H. Horinouchi, H. Harada, T. Sobue, T. Kato, S. Atagi, T. Kozuki, T. Tokito, S. Oizumi, M. Seike, K. Ohashi, T. Mio, T. Sone, M. Jinushi, M. Tsuboi, Deciphering the clinical features of heterogeneous stage III non-small cell lung cancer in Japanese real-world clinical practice: Expanded cohort of the SOLUTION study, Lung Cancer 165 (2022) 152–163.

H. Horinouchi, S. Atagi, S. Oizumi, K. Ohashi, T. Kato, T. Kozuki, M. Seike, T. Sone, T. Sobue, T. Tokito, H. Harada, T. Maeda, T. Mio, I. Shirosaka, K. Hattori, E. Shin, H. Murakami, Real-world outcomes of chemoradiotherapy for unresectable Stage III non-small cell lung cancer: The SOLUTION study, Cancer Med. 9 (2020) 6597–6608.

CRediT authorship contribution statement

Hidehito Horinouchi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Haruyasu Murakami:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Hideyuki Harada:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Tomotaka Sobue:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Tomohiro Kato:** Conceptualization, Data curation, Investigation, Visualization, Writing – review & editing. **Shinji Atagi:** Conceptualization, Data curation, Investigation, Visualization, Writing – review & editing. **Toshiyuki Kozuki:** Conceptualization, Data curation, Investigation, Visualization, Writing – review & editing. **Takaaki Tokito:** Conceptualization, Data curation, Investigation, Visualization, Writing – review & editing. **Satoshi Oizumi:** Conceptualization, Data

curation, Investigation, Visualization, Writing – review & editing. **Masahiro Seike:** Conceptualization, Data curation, Investigation, Visualization, Writing – review & editing. **Kadoaki Ohashi:** Conceptualization, Data curation, Investigation, Visualization, Writing – review & editing. **Tadashi Mio:** Conceptualization, Data curation, Investigation, Visualization, Writing – review & editing. **Takashi Sone:** Conceptualization, Data curation, Investigation, Visualization, Writing – review & editing. **Chikako Iwao:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Takeshi Iwane:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ryo Koto:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Masahiro Tsuboi:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hidehito Horinouchi reported research funds from MSD, AbbVie, AstraZeneca, Bristol-Myers Squibb, Ono, Merck Biopharma, Daiichi Sankyo, Janssen, Genomic Health, Chugai, Roche, and Novartis; honoraria from AstraZeneca, MSD, Eli Lilly, Ono, Bristol-Myers Squibb, Chugai, Roche, Kyowa Kirin, and Novartis; and serves on advisory boards for AstraZeneca, Eli Lilly, Chugai, Roche, Ono, Bristol-Myers Squibb, and MSD.

Haruyasu Murakami reported support for the present manuscript from AstraZeneca; reported institutional research grants/funding from Chugai, AstraZeneca, AbbVie, Daiichi Sankyo, IQVIA, Taiho, and Bayer; honoraria from Chugai, Daiichi Sankyo, AstraZeneca, Takeda, Amgen, Ono, Bristol-Myers Squibb, MSD, Pfizer, Novartis, Eli Lilly, Taiho, Eisai, and Nippon Kayaku; and is a member of advisory boards for Chugai, GAIA BioMedicine, Daiichi Sankyo, Takeda, and Kyowa Kirin.

Hideyuki Harada reported support for the present manuscript from AstraZeneca; and lecture fees from Hitachi, AstraZeneca, Brainlab, Accuray, Chugai, Eisai, Taiho, Takeda, Pfizer, MSD, and Nihon Medi-Physics.

Tomotaka Sobue reported no conflicts of interest.

Tomohiro Kato reported payments or honoraria from AstraZeneca, Chugai, Kyowa Kirin, Eli Lilly, MSD, Boehringer Ingelheim, Taiho, Ono, Nippon Kayaku, Takeda, and Novartis.

Shinji Atagi reported support for the present manuscript from AstraZeneca; and grants from AstraZeneca, Eli Lilly, Ono, Taiho, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, MSD, Chugai, Merck, and F. Hoffmann-La Roche.

Toshiyuki Kozuki reported institutional funding from Chugai, AstraZeneca, Eli Lilly, Taiho, Bristol-Myers Squibb, Ono, MSD, Kyowa Kirin, Merck Biopharma, Daiichi Sankyo, Amgen, AbbVie, Sanofi, Eisai, Labcorp Development Japan, IQVIA, Gilead Sciences, Pfizer, and Bayer; consulting fees from Chugai, AstraZeneca, Ono, Pfizer, Daiichi Sankyo, Bayer, and AbbVie; and payments or honoraria from Chugai, AstraZeneca, Eli Lilly, Taiho, Bristol-Myers Squibb, Ono, MSD, Pfizer, Kyowa Kirin, Boehringer Ingelheim, Merck Biopharma, Nippon Kayaku, Novartis, Daiichi Sankyo, Takeda, Bayer, Sawai, Amgen, and Eisai.

Takaaki Tokito reported honoraria for lectures from Chugai, AstraZeneca, MSD, Novartis, and Bristol-Myers Squibb.

Satoshi Oizumi reported grants from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Chugai, Pfizer, MSD, Sanofi, Taiho, and Takeda; and payments or honoraria from AstraZeneca, Chugai, MSD, and Takeda.

Masahiro Seike reported lecture fees from AstraZeneca, MSD, Chugai, Taiho, Nippon Kayaku, Ono, Bristol-Myers Squibb, Eli Lilly, Takeda, Kyowa Kirin, and Novartis; and special donations from Taiho, MSD, Chugai, Eli Lilly, Nippon Kayaku, and Boehringer Ingelheim.

Kadoaki Ohashi reported support for the present manuscript from AstraZeneca; and payment or honoraria from AstraZeneca.

Tadashi Mio reported no conflicts of interest.

Takashi Sone reported no conflicts of interest.

Chikako Iwao is an employee of AstraZeneca.

Takeshi Iwane is an employee of AstraZeneca.

Ryo Koto is an employee of AstraZeneca.

Masahiro Tsuboi reported support for data collection for this study from AstraZeneca; institutional grants from MSD, AstraZeneca, Bristol-Myers Squibb, Ono, Eli Lilly, Novartis, and MiRXES; lecture fees from Johnson & Johnson, Medtronic, AstraZeneca, Eli Lilly, Chugai, Taiho, Bristol-Myers Squibb, Ono, Novalis, MSD, and Daiichi Sankyo; and is a member of a data safety monitoring board for Chugai and advisory boards for AstraZeneca, MSD, Novartis, and MiRXES; and is a member of the Board of Directors of the Japan Lung Cancer Society.

Acknowledgments

The authors thank all the clinicians who participated in this study. This study was funded by AstraZeneca K.K. The authors thank Nicholas D. Smith (EMC K.K.) for medical writing support, which was funded by AstraZeneca K.K.

Role of the funding source

AstraZeneca K.K. funded the study, the publication, and medical writing support. The sponsor contributed to study design, data collection, data analysis, data interpretation, and manuscript review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2024.108027.

Data availability

Data underlying the findings described in this study may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

References

[1] N. Sawabata, E. Miyaoka, H. Asamura, Y. Nakanishi, K. Eguchi, M. Mori, H. Nomori, Y. Fujii, M. Okumura, K. Yokoi, Japanese Lung Cancer Registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade, J. Thorac. Oncol. 6 (2011) 1229–1235, https://doi.org/10.1097/JTO.0b013e318219aae2.

[2] I. Yoshino, S. Yoshida, E. Miyaoka, H. Asamura, H. Nomori, Y. Fujii, Y. Nakanishi, K. Eguchi, M. Mori, N. Sawabata, M. Okumura, K. Yokoi, Surgical outcome of stage IIIA- cN2/pN2 non-small-cell lung cancer patients in Japanese Lung Cancer Registry study in 2004, J. Thorac. Oncol. 7 (2012) 850–855.

[3] H. Decaluwé, P. De Leyn, J. Vansteenkiste, C. Dooms, D. Van Raemdonck, P. Nafteux, W. Coosemans, T. Lerut, Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival, Eur. J. Cardiothorac. Surg. 36 (2009) 433–439.

[4] J. Hancock, J. Rosen, A. Moreno, A.W. Kim, F.C. Detterbeck, D.J. Boffa, Management of clinical stage IIIA primary lung cancers in the National Cancer Database, Ann. Thorac. Surg. 98 (2014) 424–432, discussion 432.

[5] A. Herskovic, E. Mauer, P. Christos, H. Nagar, Role of postoperative radiotherapy in pathologic stage IIIA (N2) non-small cell lung cancer in a prospective nationwide oncology outcomes database, J. Thorac. Oncol. 12 (2017) 302–313.
[6] H. Horinouchi, Y. Goto, S. Kanda, Y. Fujiwara, H. Nokihara, N. Yamamoto, M. Sumi, T. Tamura, Y. Ohe, Candidates for intensive local treatment in cIIIA-N2 non-small cell lung cancer: deciphering the heterogeneity, Int. J. Radiat. Oncol. Biol. Phys. 94 (2016) 155–162.
[7] M. Inoue, N. Sawabata, S. Takeda, M. Ohta, Y. Ohno, H. Maeda, Results of surgical intervention for p-stage IIIA (N2) non-small cell lung cancer: acceptable prognosis predicted by complete resection in patients with single N2 disease with primary tumor in the upper lobe, J. Thorac. Cardiovasc. Surg. 127 (2004) 1100–1106.
[8] M. Koshy, S.A. Fedewa, R. Malik, M.K. Ferguson, W.T. Vigneswaran, L. Feldman, A. Howard, K. Abdelhady, R.R. Weichselbaum, K.S. Virgo, Improved survival associated with neoadjuvant chemoradiation in patients with clinical stage IIIA (N2) non-small-cell lung cancer, J. Thorac. Oncol. 8 (2013) 915–922.
[9] A.P. Patel, T.D. Crabtree, J.M. Bell, T.J. Guthrie, C.G. Robinson, D. Morgensztern, G.A. Colditz, D. Kreisel, A.S. Krupnick, J.D. Bradley, G.A. Patterson, B.F. Meyers, V. Puri, National patterns of care and outcomes after combined modality therapy for stage IIIA non-small-cell lung cancer, J. Thorac. Oncol. 9 (2014) 612–621.
[10] S. Paul, F. Mirza, J.L. Port, P.C. Lee, B.M. Stiles, A.L. Kansler, N.K. Altorki, Survival of patients with clinical stage IIIA non-small cell lung cancer after induction therapy: age, mediastinal downstaging, and extent of pulmonary resection as independent predictors, J. Thorac. Cardiovasc. Surg. 141 (2011) 48–58.
[11] M. Pless, R. Stupp, H.B. Ris, R.A. Stahel, W. Weder, S. Thierstein, M.A. Gerard, A. Xyrafas, M. Früh, R. Cathomas, A. Zippelius, A. Roth, M. Bijelovic, A. Ochsenbein, U.R. Meier, C. Mamot, D. Rauch, O. Gautschi, D.C. Betticher, R. O. Mirimanoff, S. Peters, Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial, Lancet 386 (2015) 1049–1056.
[12] C.G. Robinson, A.P. Patel, J.D. Bradley, T. DeWees, S.N. Waqar, D. Morgensztern, M.Q. Baggstrom, R. Govindan, J.M. Bell, T.J. Guthrie, G.A. Colditz, T.D. Crabtree, D. Kreisel, A.S. Krupnick, G.A. Patterson, B.F. Meyers, V. Puri, Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the National Cancer Data Base, J. Clin. Oncol. 33 (2015) 870–876, https://doi.org/10.1200/JCO.2014.58.5380.
[13] A. Swaminath, E.T. Vella, K. Ramchandar, A. Robinson, C. Simone, A. Sun, Y. C. Ung, K. Yasufuku, P.M. Ellis, Surgery after chemoradiotherapy in patients with stage III (N2 or N3, excluding T4) non-small-cell lung cancer: a systematic review, Curr. Oncol. 26 (2019) e398–e404, https://doi.org/10.3747/co.26.4549.
[14] J.P. van Meerbeeck, G.W. Kramer, P.E. Van Schil, C. Legrand, E.F. Smit, F. Schramel, V.C. Tjan-Heijnen, B. Biesma, C. Debruyne, N. van Zandwijk, T. A. Splinter, G. Giaccone, Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer, J. Natl Cancer Inst. 99 (2007) 442–450.
[15] F. Couñago, N. Rodriguez de Dios, S. Montemuiño, J. Jové-Teixidó, M. Martin, P. Calvo-Crespo, M. López-Mata, M.P. Samper-Ots, J.L. López-Guerra, T. García-Cañibano, V. Díaz-Díaz, L. de Ingunza-Barón, M. Murcia-Mejía, P. Alcántara, J. Corona, M.M. Puertas, M. Chust, M.L. Couselo, E. del Cerro, J. Moradiellos, S. Amor, A. Varela, I.J. Thuissard, D. Sanz-Rosa, B. Taboada, Neoadjuvant treatment followed by surgery versus definitive chemoradiation in stage IIIA-N2 non-small-cell lung cancer: a multi-institutional study by the Oncologic Group for the Study of Lung Cancer (Spanish Radiation Oncology Society), Lung Cancer 118 (2018) 119–127.
[16] G.E. Darling, F. Li, D. Patsios, C. Massey, A.G. Wallis, L. Coate, S. Keshavjee, A. Pierre, M. De Perrot, K. Yasufuku, M. Cypel, T. Waddell, Neoadjuvant chemoradiation and surgery improves survival outcomes compared with definitive chemoradiation in the treatment of stage IIIA N2 non-small-cell lung cancer, Eur. J. Cardiothorac. Surg. 48 (2015) 684–690, discussion 690.
[17] X.L. Xu, L. Dan, W. Chen, S.M. Zhu, W.M. Mao, Neoadjuvant chemoradiotherapy or chemotherapy followed by surgery is superior to that followed by definitive chemoradiation or radiotherapy in stage IIIA (N2) nonsmall-cell lung cancer: a meta-analysis and system review, Onco Targets Ther. 9 (2016) 845–853, https://doi.org/10.2147/ott.s95511.
[18] P.M. Putora, P. Leskow, F. McDonald, T. Batchelor, M. Evison, International guidelines on stage III N2 nonsmall cell lung cancer: surgery or radiotherapy? ERJ Open Res. 6 (2020) https://doi.org/10.1183/23120541.00159-2019, 00159-2019.
[19] S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Kurata, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Faivre-Finn, M. Reck, J. Vansteenkiste, D.R. Spigel, C. Wadsworth, G. Melillo, M. Taboada, P.A. Dennis, M. Özgüroğlu, Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, N. Engl. J. Med. 379 (2018) 2342–2350.
[20] S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, M. Özgüroğlu, Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer, N. Engl. J. Med. 377 (2017) 1919–1929.
[21] N. Girard, J. Bar, P. Garrido, M.C. Garassino, F. McDonald, F. Mornex, A.R. Filippi, H.J.M. Smit, S. Peters, J.K. Field, D.C. Christoph, A. Sibille, R. Fietkau, V. D. Haakensen, C. Chouaid, B. Markman, T.J.N. Hiltermann, A. Taus, W. Sawyer, A. Allen, P. Chander, M. Licour, B. Solomon, Treatment characteristics and real-world progression-free survival in patients with unresectable Stage III NSCLC who received durvalumab after chemoradiotherapy: findings from the PACIFIC-R study, J. Thorac. Oncol. 18 (2023) 181–193.
[22] E. Felip, N. Altorki, C. Zhou, T. Csőszi, I. Vynnychenko, O. Goloborodko, A. Luft, A. Akopov, A. Martinez-Marti, H. Kenmotsu, Y.M. Chen, A. Chella, S. Sugawara, D. Voong, F. Wu, J. Yi, Y. Deng, M. McCleland, E. Bennett, B. Gitlitz, H. Wakelee, Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial, Lancet 398 (2021) 1344–1357.
[23] P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S. R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.E. Ciuleanu, G. B. Saylors, F. Tanaka, H. Ito, K.N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C. Y. Calvet, N. Girard, Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer, N. Engl. J. Med. 386 (2022) 1973–1985.
[24] H. Murakami, H. Horinouchi, H. Harada, T. Sobue, T. Kato, S. Atagi, T. Kozuki, T. Tokito, S. Oizumi, M. Seike, K. Ohashi, T. Mio, T. Sone, M. Jinushi, M. Tsuboi, Deciphering the clinical features of heterogeneous stage III non-small cell lung cancer in Japanese real-world clinical practice: Expanded cohort of the SOLUTION study, Lung Cancer 165 (2021) 152–163, https://doi.org/10.1016/j.lungcan.2021.12.005.
[25] H. Horinouchi, S. Atagi, S. Oizumi, K. Ohashi, T. Kato, T. Kozuki, M. Seike, T. Sone, T. Sobue, T. Tokito, H. Harada, T. Maeda, T. Mio, I. Shirosaka, K. Hattori, E. Shin, H. Murakami, Real-world outcomes of chemoradiotherapy for unresectable Stage III non-small cell lung cancer: The SOLUTION study, Cancer Med. 9 (2020) 6597–6608.
[26] Ministry of Health, Labour and Welfare, Ethical Guidelines for Medical and Health Research Involving Human Subjects (provisional English translation, March 2015). Amended February 28, 2017. Available at: https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf. Accessed: November 25, 2024.
[27] S.B. Edge, D.R. Byrd, C.C. Compton, A.G. Fritz, F.L. Greene, A. Trotti (Eds.), AJCC Cancer Staging Manual, seventh ed., Springer, New York, 2010 https://www.facs.org/media/j30havyf/ajcc_7thed_cancer_staging_manual.pdf.
[28] Japan Lung Cancer Society, General Rule for Clinical and Pathological Record of Lung Cancer, eighth ed., Kanehara, Tokyo, Japan, 2017.
[29] N. Altorki, X. Wang, D. Kozono, C. Watt, R. Landrenau, D. Wigle, J. Port, D. R. Jones, M. Conti, A.S. Ashrafi, M. Liberman, K. Yasufuku, S. Yang, J.D. Mitchell, H. Pass, R. Keenan, T. Bauer, D. Miller, L.J. Kohman, T.E. Stinchcombe, E. Vokes, Lobar or sublobar resection for peripheral Stage IA non-small-cell lung cancer, N. Engl. J. Med. 388 (2023) 489–498.
[30] H. Saji, M. Okada, M. Tsuboi, R. Nakajima, K. Suzuki, K. Aokage, T. Aoki, J. Okami, I. Yoshino, H. Ito, N. Okumura, M. Yamaguchi, N. Ikeda, M. Wakabayashi, K. Nakamura, H. Fukuda, S. Nakamura, T. Mitsudomi, S.I. Watanabe, H. Asamura, Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial, Lancet 399 (2022) 1607–1617.
[31] K. Suzuki, S.I. Watanabe, M. Wakabayashi, H. Saji, K. Aokage, Y. Moriya, I. Yoshino, M. Tsuboi, S. Nakamura, K. Nakamura, T. Mitsudomi, H. Asamura, A single-arm study of sublobar resection for ground-glass opacity dominant peripheral lung cancer, J. Thorac. Cardiovasc. Surg. 163 (2022) 289–301.e2.
[32] S. Atagi, M. Kawahara, A. Yokoyama, H. Okamoto, N. Yamamoto, Y. Ohe, T. Sawa, S. Ishikura, T. Shibata, H. Fukuda, N. Saijo, T. Tamura, Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301), Lancet Oncol. 13 (2012) 671–678.
[33] C. Geng, H. Paganetti, C. Grassberger, Prediction of treatment response for combined chemo- and radiation therapy for non-small cell lung cancer patients using a bio-mathematical model, Sci. Rep. 7 (2017) 13542, https://doi.org/10.1038/s41598-017-13646-z.
[34] Y. Segawa, K. Kiura, N. Takigawa, H. Kamei, S. Harita, S. Hiraki, Y. Watanabe, K. Sugimoto, T. Shibayama, T. Yonei, H. Ueoka, M. Takemoto, S. Kanazawa, I. Takata, N. Nogami, K. Hotta, A. Hiraki, M. Tabata, K. Matsuo, M. Tanimoto, Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007, J. Clin. Oncol. 28 (2010) 3299–3306, https://doi.org/10.1200/jco.2009.24.7577.
[35] N. Yamamoto, K. Nakagawa, Y. Nishimura, K. Tsujino, M. Satouchi, S. Kudo, T. Hida, M. Kawahara, K. Takeda, N. Katakami, T. Sawa, S. Yokota, T. Seto, F. Imamura, H. Saka, Y. Iwamoto, H. Semba, Y. Chiba, H. Uejima, M. Fukuoka, Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105, J. Clin. Oncol. 28 (2010) 3739–3745, https://doi.org/10.1200/jco.2009.24.5050.
[36] M. Isaka, H. Kojima, S. Takahashi, K. Omae, Y. Ohde, Risk factors for local recurrence after lobectomy and lymph node dissection in patients with non-small cell lung cancer: Implications for adjuvant therapy, Lung Cancer 115 (2018) 28–33.
[37] T. Maniwa, S. Takahashi, M. Isaka, M. Endo, Y. Ohde, Outcomes of initial surgery in patients with clinical N2 non-small cell lung cancer who met 4 specific criteria, Surg. Today 46 (2016) 699–704.
[38] A. Scherpereel, E. Martin, L. Brouchet, R. Corre, M. Duruisseaux, P.E. Falcoz, P. Giraud, C. Le Péchoux, M. Wislez, M. Alifano, Reaching multidisciplinary consensus on the management of non-bulky/non-infiltrative stage IIIA N2 non-small cell lung cancer, Lung Cancer 177 (2023) 21–28.
[39] K. Park, J. Vansteenkiste, K.H. Lee, G. Pentheroudakis, C. Zhou, K. Prabhash, T. Seto, P.J. Voon, D.S.W. Tan, J.C.H. Yang, J. Wang, K.G. Babu, Y. Nakayama, A. Alip, K.L.M. Chua, J.C. Cheng, S. Senan, Y.C. Ahn, T.Y. Kim, H.K. Ahn, S. Peters, T. Yoshino, J.Y. Douillard, Pan-Asian adapted ESMO Clinical Practice Guidelines

for the management of patients with locally-advanced unresectable non-small-cell lung cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS, Ann. Oncol. 31 (2020) 191–201.
[40] Japan Lung Cancer Society, Clinical Guideline for the Management of Lung Cancer, 2022. Available from: https://www.haigan.gr.jp/publication/guideline/examination/2022/. Accessed: November 25, 2024 (in Japanese).
[41] A.T. Arndt, A little bit of cancer is still cancer: is it time for lymph node micrometastases in non-small cell lung cancer to get their due? Ann. Surg. Oncol. 25 (2018) 3781–3782.
[42] A.R. Belanger, J. Hollyfield, G. Yacovone, A.S. Ceppe, J.A. Akulian, A.C. Burks, M. P. Rivera, L.G. Dodd, J.M. Long, B.E. Haithcock, C.V. Pecot, Incidence and clinical relevance of non-small cell lung cancer lymph node micro-metastasis detected by staging endobronchial ultrasound-guided transbronchial needle aspiration, J. Thorac. Dis. 11 (2019) 3650–3658.
[43] Y. Ren, L. Zhang, H. Xie, Y. She, H. Su, D. Xie, H. Zheng, L. Zhang, G. Jiang, C. Wu, C. Dai, C. Chen, Lymph node micrometastasis prognosticates survival for patients with stage 1 bronchogenic adenocarcinoma, Ann. Surg. Oncol. 25 (2018) 3812–3819.
[44] S. Katsumata, K. Aokage, G. Ishii, S. Nakasone, T. Sakai, S. Okada, T. Miyoshi, K. Tane, M. Tsuboi, Prognostic impact of the number of metastatic lymph nodes on the Eighth Edition of the TNM Classification of NSCLC, J. Thorac. Oncol. 14 (2019) 1408–1418.
[45] J. Samejima, H. Ito, T. Nagashima, D. Nemoto, D. Eriguchi, H. Nakayama, N. Ikeda, M. Okada, Anatomical location and number of metastatic lymph nodes for prognosis of non-small cell lung cancer, J. Thorac. Dis. 13 (2021) 4083–4093.
[46] C. Yoo, S. Yoon, D.H. Lee, S.I. Park, D.K. Kim, Y.H. Kim, H.R. Kim, S.H. Choi, W. S. Kim, C.M. Choi, S.J. Jang, S.Y. Song, S.S. Kim, E.K. Choi, J.C. Lee, C. Suh, J. S. Lee, S.W. Kim, Prognostic significance of the number of metastatic pN2 lymph nodes in stage IIIA-N2 non-small-cell lung cancer after curative resection, Clin. Lung Cancer 16 (2015) e203–e212.
[47] A.M. Bell, B.R. DeYoung, J. Weydert, Extranodal extension in metastatic non-small cell lung cancer, Chest 132 (2007) 2058–2059, author reply 2059–2060.
[48] Y.C. Lee, C.T. Wu, S.W. Kuo, Y.T. Tseng, Y.L. Chang, Significance of extranodal extension of regional lymph nodes in surgically resected non-small cell lung cancer, Chest 131 (2007) 993–999.
[49] B.C. Shih, J.H. Jeon, J.H. Chung, H.J. Kwon, J.H. Lee, W. Jung, Y. Hwang, S. Cho, K. Kim, S. Jheon, Prognostic significance of the extranodal extension of regional lymph nodes in stage III-N2 non-small-cell lung cancer after curative resection, J. Clin. Med. 10 (2021) 3324.
[50] A. Ardizzoni, L. Boni, M. Tiseo, F.V. Fossella, J.H. Schiller, M. Paesmans, D. Radosavljevic, A. Paccagnella, P. Zatloukal, P. Mazzanti, D. Bisset, R. Rosell, Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis, J. Natl Cancer Inst. 99 (2007) 847–857.
[51] S. Bailey, Q. Wang, C.Y. Kong, K. Stone, R. Veluswamy, S.E. Bates, C.B. Smith, J. P. Wisnivesky, K. Sigel, Optimizing the use of adjuvant chemotherapy in non-small cell lung cancer patients with comorbidities, Curr. Probl. Cancer 46 (2022) 100867.
[52] R.S. Herbst, P. Baas, D.W. Kim, E. Felip, J.L. Pérez-Gracia, J.Y. Han, J. Molina, J. H. Kim, C.D. Arvis, M.J. Ahn, M. Majem, M.J. Fidler, G. de Castro Jr., M. Garrido, G.M. Lubiniecki, Y. Shentu, E. Im, M. Dolled-Filhart, E.B. Garon, Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, Lancet 387 (2016) 1540–1550.
[53] J.V. Heymach, D. Harpole, T. Mitsudomi, J.M. Taube, G. Galffy, M. Hochmair, T. Winder, R. Zukov, G. Garbaos, S. Gao, H. Kuroda, J. You, K.-Y. Lee, L. Antonuzzo, M. Aperghis, G.J. Doherty, H. Mann, T.M. Fouad, M. Reck, Abstract CT005: AEGEAN: A phase 3 trial of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in patients with resectable NSCLC, Cancer Res. 83 (2023) CT005, https://doi.org/10.1158/1538-7445.AM2023-CT005.
[54] M. O'Brien, L. Paz-Ares, S. Marreaud, U. Dafni, K. Oselin, L. Havel, E. Esteban, D. Isla, A. Martinez-Marti, M. Faehling, M. Tsuboi, J.S. Lee, K. Nakagawa, J. Yang, A. Samkari, S.M. Keller, M. Mauer, N. Jha, R. Stahel, B. Besse, S. Peters, Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial, Lancet Oncol. 23 (2022) 1274–1286.
[55] M.I. Ronden, I. Bahce, N.J.M. Claessens, N. Barlo, M.R. Dahele, J.M.A. Daniels, C. Tissing-Tan, E. Hekma, S.M.S. Hashemi, A. van der Wel, F.O.B. Spoelstra, W. Verbakel, M.A. Tiemessen, M. van Laren, A. Becker, S. Tarasevych, C.J. A. Haasbeek, K. Maassen van den Brink, C. Dickhoff, S. Senan, The impact of the availability of immunotherapy on patterns of care in Stage III NSCLC: a Dutch multicenter analysis, JTO Clin. Res. Rep. 2 (2021) 100195.
[56] N. Waser, L. Vo, M. McKenna, J.R. Penrod, S. Goring, Real-world treatment patterns in resectable (stages I–III) non-small-cell lung cancer: a systematic literature review, Future Oncol. 18 (2022) 1519–1530.
[57] WCLC attendees hear preview of proposed changes for the 9th edition of the TNM staging classification for thoracic cancers. Press release, October 10, 2023. Available from: https://www.ilcn.org/wclc-attendees-hear-preview-of-proposed-changes-for-the-9th-edition-of-the-tnm-staging-classification-for-thoracic-cancers/. Accessed: November 25, 2024.