Cancer Chemotherapy and Pharmacology (2019) 84:275–280
https://doi.org/10.1007/s00280-019-03885-4

ORIGINAL ARTICLE

Ineligibility for the PACIFIC trial in unresectable stage III non-small cell lung cancer patients

Kazutaka Hosoya[1] · Daichi Fujimoto[1] · Hayato Kawachi[1] · Yuki Sato[1] · Mariko Kogo[1] · Kazuma Nagata[1] · Atsushi Nakagawa[1] · Ryo Tachikawa[1] · Shinya Hiraoka[2] · Masaki Kokubo[2] · Keisuke Tomii[1]

Received: 20 February 2019 / Accepted: 4 June 2019 / Published online: 14 June 2019

Abstract

Purpose Recently, based on results of the PACIFIC trial, durvalumab after chemoradiotherapy (CRT) became the standard therapy for unresectable stage III non-small cell lung cancer (NSCLC). However, in the PACIFIC trial, patients were recruited and randomized after CRT, and certain patients were considered ineligible after CRT in the real world. No study has been conducted on the patients who were ineligible for the PACIFIC trial, and hence, we conducted a retrospective study on them.

Methods We identified 82 patients with stage III NSCLC who received definitive platinum-based concurrent CRT and had World Health Organization performance status of 0–1. We investigated the proportion, clinical characteristics, and prognoses of patients who became ineligible for the PACIFIC trial after CRT.

Results After CRT, 19 of 82 patients (23%) became ineligible for the PACIFIC trial. Comparison between eligible and ineligible patients revealed that old age ($p=0.042$), male gender ($p=0.031$), and radiation therapy with V20 ≥ 35% ($p=0.032$) were associated with ineligibility after CRT. Moreover, ineligible patients showed shorter PFS (6.6 vs. 15.7 months, hazard ratio [HR] 2.61, 95% confidence interval [CI] 1.16–5.89, $p=0.016$) and shorter OS (18.6 vs. 44.3 months, HR 3.03, 95% CI 1.29–7.10, $p=0.007$) than eligible patients.

Conclusions Our study revealed the clinical characteristics and prognoses of patients who became ineligible for the PACIFIC trial after CRT. Physicians should be careful while prescribing CRT for patients with characteristics such as old age, male gender, and radiation therapy with V20 ≥ 35%.

Keywords Non-small cell lung cancer · Definitive chemoradiotherapy · Durvalumab · Eligibility criteria · Outcome

Introduction

Lung cancer is the leading cause of cancer deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 80% of the lung cancer cases, of which approximately 20–30% cases are classified as stage III [2, 3]. Up to 30–50% of stage III NSCLCs are unresectable at the time of diagnosis. For 2 decades, concurrent chemoradiation therapy (CRT) has been the standard therapy for unresectable stage III NSCLC [4]. Recently, the PACIFIC trial results showed that administration of durvalumab, an anti-programmed death ligand 1 monoclonal antibody, after CRT to unresectable stage III NSCLC patients significantly prolonged progression-free survival (PFS) and overall survival (OS) compared with placebo administration [5, 6]; this has now become the standard therapy.

However, in the PACIFIC trial, patients were recruited and randomized after definitive platinum-based concurrent CRT and not before CRT. Subsequently, among patients with unresectable stage III NSCLC who started CRT, only limited patients in better status should have been included in the PACIFIC trial. No study has been conducted on the proportion and clinical characteristics of patients who were ineligible for the PACIFIC trial and on the reasons for ineligibility. Therefore, we conducted a retrospective study on the proportion, clinical characteristics, and prognoses of patients who became ineligible for the PACIFIC trial after

✉ Daichi Fujimoto
daichi@kcho.jp

[1] Department of Respiratory Medicine, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-Minamimachi, Chuo-ku, Kobe 650-0047, Japan

[2] Department of Radiation Oncology, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-Minamimachi, Chuo-ku, Kobe 650-0047, Japan

CRT to identify areas that could be improved with respect to treatment for this patient group.

Materials and methods

Patients

We identified 98 patients with stage III NSCLC who received definitive concurrent CRT between January 2009 and July 2017 in Kobe City Medical Center General Hospital. World Health Organization performance status (WHO PS) was used to indicate the performance status. Patients who reported never smoking in their life were defined as never-smokers, those who had smoked within 1 year of diagnosis were categorized as current smokers, and the remaining patients were classified as ex-smokers. The clinical stage of all patients was established according to the 7th edition of the tumor, node, and metastasis (TNM) classification. Disease progression was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. All toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. This study protocol was approved by the ethics committee of Kobe City Medical Center General Hospital.

Eligibility criteria for the PACIFIC trial

Patients who fulfilled all the following criteria were defined as eligible at CRT initiation: age 18 years or older, presence of histologically or cytologically documented stage III NSCLC (according to the 7th edition of the TNM classification), scheduled to receive platinum-based chemotherapy concurrent with radiation therapy, WHO PS scores of 0–1, receipt of no immunotherapy, no history of immunosuppressive medication use, no recent major surgery, no active or previously documented autoimmune diseases, no active or previously documented inflammatory bowel diseases, no other active intercurrent illnesses, and no current participation in interventional clinical studies. Additionally, the patients who fulfilled all the following criteria were defined as eligible after CRT termination: received at least two cycles of platinum-based chemotherapy concurrent with radiation therapy, no disease progression or death within 42 days of radiation therapy completion, WHO PS scores of 0–1, no blood cell abnormalities (absolute neutrophil count $> 1.5 \times 10^9$/L; platelet count $> 100 \times 10^9$/L; hemoglobin level ≥ 9.0 g/dL), no renal failure (serum creatinine clearance > 40 mL/min using the Cockcroft–Gault formula), no liver failure (serum bilirubin level < 1.5 × upper limit of the normal range; aspartate aminotransferase and alanine aminotransferase levels < 2.5 × upper limit of the normal range), no unresolved > CTCAE grade 2 toxicity due to CRT, and no ≥ grade 2 pneumonitis due to CRT. All the eligibility criteria following CRT were evaluated within 42 days of radiation therapy termination.

We modified the inclusion and exclusion criteria used in the PACIFIC trial to suit the retrospective nature of our study. Of the inclusion and exclusion criteria used in the PACIFIC trial, we did not evaluate criteria related to life expectancy, reproduction, and electrocardiogram abnormalities. This was because we could not evaluate life expectancy and reproduction, and because electrocardiograms were not routinely examined just before CRT. In the PACIFIC

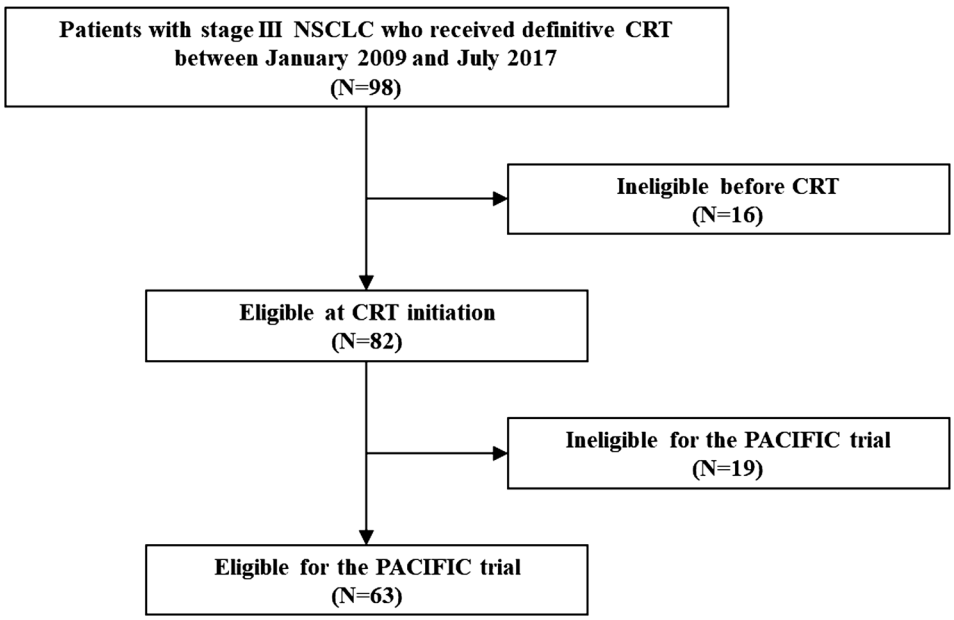

Fig. 1 Flowchart of the study patients

trial, recovery from CRT-associated toxicities was judged within 42 days of CRT termination. However, because some patients received consolidation chemotherapy after CRT in this study, we could only judge recovery from toxicities within 42 days of radiation therapy termination (not CRT termination).

Statistical analysis

The correlation between age and eligibility was analyzed using the Wilcoxon rank-sum test. Dichotomous variables were analyzed using the Chi-square or Fisher's exact test, as appropriate. PFS and OS were estimated using the Kaplan–Meier method and compared using the Log-rank test. Statistical analyses were conducted using JMP software (version 14; SAS Institute, Cary, NC, USA). For all analyses, a two-tailed p value of < 0.05 was considered significant.

Results

Patient characteristics and reasons for ineligibility

Of the 98 stage III NSCLC patients who received definitive concurrent CRT, 16 were excluded because they received monotherapy regimens as chemotherapy and/or had poor WHO PS. A total of 82 patients were eligible at CRT initiation (Fig. 1). Of the 82 patients, 63 (77%) were eligible after CRT and 19 (23%) became ineligible after CRT. Patient characteristics and comparisons between eligible and ineligible patients are summarized in Table 1. The reasons for ineligibility were as follows: seven patients showed disease progression within 42 days of radiation therapy termination, six had ≥ grade 2 pneumonitis (including one who died from pneumonitis within 42 days of radiation termination), four received only one cycle of platinum-based chemotherapy due to adverse events, one showed deterioration in PS, and one developed grade 2 renal failure after the concurrent phase. Moreover, four patients received only one cycle of platinum-based chemotherapy for the following reasons: one patient had grade 3 febrile neutropenia, one had grade 3 neutropenia, one had grade 3 creatinine level elevation, and one had grade 3 bacterial pneumonia. Of the 82 patients, 60 (73%) received consolidation chemotherapy.

Comparison between eligible and ineligible patients

As shown in Table 1, comparison between eligible and ineligible patients revealed that old age ($p = 0.042$), male gender ($p = 0.031$), and radiation therapy with V20 ≥ 35% ($p = 0.032$) were associated with ineligibility after the concurrent phase. On analysis of PFS and OS, we excluded eight ineligible patients who showed disease progression or death within 42 days of radiation therapy termination (Figs. 2 and 3). Ineligible patients showed shorter PFS (6.6 vs. 15.7 months, HR 2.61, 95% confidence interval [CI] 1.16–5.89, $p = 0.016$) and shorter OS (18.6 vs. 44.3 months, HR 3.03, 95% CI 1.29–7.10, $p = 0.007$) than eligible patients. There was no significant difference in the proportion of patients who received consolidation chemotherapy between ineligible patients and eligible patients (64% and 81%, respectively, $p = 0.21$).

Table 1 Patient characteristics and comparisons between eligible and ineligible patients after chemoradiotherapy

Characteristics	All ($n = 82$)	Eligible ($n = 63$)	Ineligible ($n = 19$)	p value
Age (years)				
Median (range)	69 (36–83)	67 (36–83)	72 (53–79)	0.042**
Sex, *N* (%)				
Male	69 (84)	50 (79)	19 (100)	0.031**
Female	13 (16)	13 (21)	0	
WHO PS, *N* (%)				
0	26 (32)	21 (33)	5 (26)	0.565
1	56 (68)	42 (67)	14 (74)	
Smoking status, *N* (%)				
Never smoker	7 (9)	7 (11)	0	0.129
Smoker	75 (91)	56 (89)	19 (100)	
Stage, *N* (%)				
III A	41 (50)	30 (48)	11 (58)	0.432
III B	41 (50)	33 (52)	8 (42)	
Histologic type, *N* (%)				
Squamous	38 (46)	27 (43)	11 (58)	0.249
Non-squamous	44 (54)	36 (57)	8 (42)	
EGFR mutation, *N* (%)				
Yes	9 (11)	9 (14)	0	0.081
No/not investigated	73 (89)	54 (86)	19 (100)	
Total dose of radiotherapy (Gy)				
Mean ± SD	60.0 ± 0.7	60.0 ± 0.0	60.1 ± 1.6	0.588
V20, *N* (%)[a]				
< 35%	73 (89)	59 (94)	14 (74)	0.032**
≥ 35%	5 (6)	2 (3)	3 (16)	
Chemotherapy regimen, *N* (%)				
CBDCA/PTX	51 (62)	39 (62)	12 (63)	
CDDP/PEM	10 (12)	9 (14)	1 (5)	
CDDP/S-1	9 (11)	6 (10)	3 (16)	
CDDP/DTX	6 (7)	5 (8)	1 (5)	
CDDP/VNR	6 (7)	4 (6)	2 (11)	

EGFR epidermal growth factor receptor, *CBDCA* carboplatin, *CDDP* cisplatin, *PTX* paclitaxel, *PEM* pemetrexed, *DTX* docetaxel, *VNR* vinorelbine, *WHO PS* World Health Organization performance status

[a]We could not calculate V20 for four patients because the data of radiation field were unusable

**$p < 0.05$

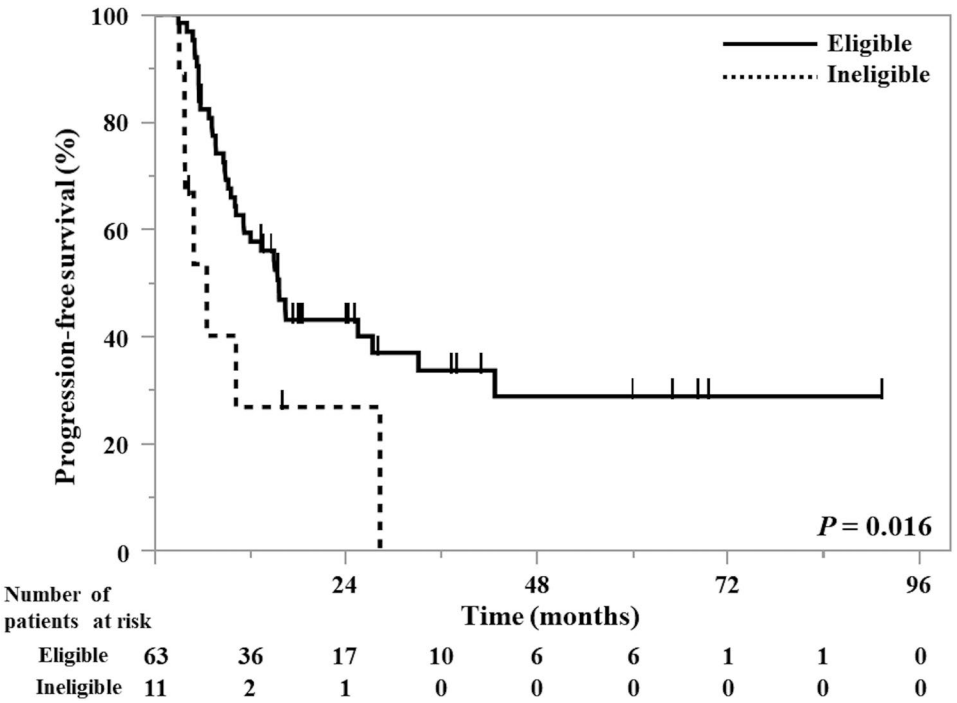

Fig. 2 Kaplan–Meier curves of progression-free survival (PFS) in eligible and ineligible patients (eight ineligible patients who showed disease progression or who died within 42 days of radiation therapy termination were excluded)

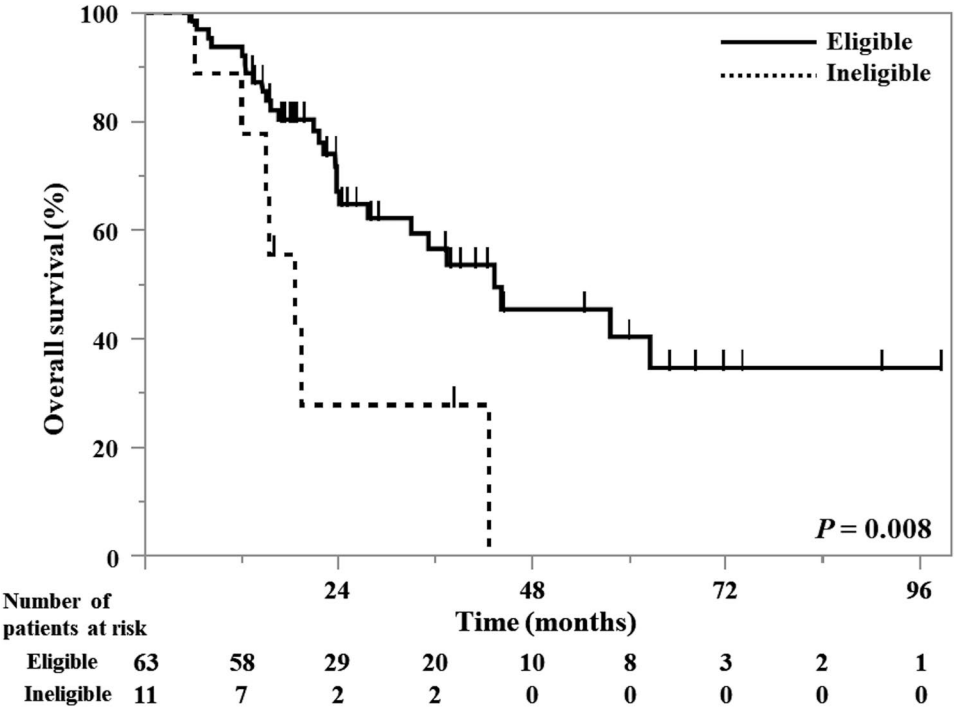

Fig. 3 Kaplan–Meier curves of overall survival (OS) in eligible and ineligible patients (eight ineligible patients who showed disease progression or who died within 42 days of radiation therapy termination were excluded)

Discussion

Our study revealed the proportion and characteristics of patients who became ineligible for the PACIFIC trial after CRT. We also found that ineligible patients showed shorter PFS and OS than eligible patients.

We found that 23% of stage III NSCLC patients who were eligible at CRT initiation became ineligible after CRT. Considering a total of 98 stage III NSCLC patients who received definitive concurrent CRT (including patients who were ineligible before CRT), 35 of 98 patients (36%) were ineligible and 63 of 98 patients (64%) were eligible after

CRT. To our knowledge, this is the first study on the proportion of unresectable stage III NSCLC patients who are ineligible for clinical trials. Previous studies have shown that 55–73% of patients who were diagnosed with advanced NSCLC (mostly stage IV, and regardless of whether they received chemotherapy) were ineligible for clinical trials [7–10]. The frequency of ineligibility in our study was relatively low compared with that of these studies; this could be because we focused on stage III NSCLC patients who were receiving CRT. The most common reason for ineligibility in our study was disease progression or death (10%); the frequency of ineligibility due to disease progression or death was reported to be 4–12% in previous clinical trials on definitive platinum-based concurrent CRT [11–14].

In our cohort, PFS and OS were shorter in ineligible patients than in eligible patients, although we excluded ineligible patients who showed disease progression or who died within 42 days of radiation therapy termination. This suggests that the eligibility for the PACIFIC trial is prognostic factor in previous standard therapy without durvalumab. In previous studies, worse conditions, such as low body mass index, poor PS, body weight loss in the concurrent phase, and interruption or reduction of chemotherapy, were shown to be prognostic factors for locally advanced NSCLC patients receiving CRT [15–18]. Furthermore, in advanced NSCLC patients, ineligibility for clinical trials was associated with poor survival outcome according to a previous study [10]. From these results, we speculated that ineligibility for the PACIFIC trial reflects poor conditions after CRT and might be a prognostic factor for conventional CRT.

Additionally, we found that old age, male gender, and radiation therapy with V20 ≥ 35% were associated with ineligibility after CRT. Of five patients who received radiation therapy with V20 ≥ 35%, three patients became ineligible after CRT; the reasons for ineligibility were disease progression (two patients) and radiation pneumonitis (one patient). The relationship between high V20 values and early disease progression is understandable considering that high V20 values inevitably result from large tumor masses. Moreover, in previous studies, high V20 values were shown to be associated with the development of radiation pneumonitis during and after CRT [19–21]; National Comprehensive Cancer Network (NCCN) guidelines recommend physicians to limit V20 to < 35% [22]. Based on these results, high V20 values seemed to be associated with ineligibility for the PACIFIC trial in our study. Physicians should recognize that patients with these factors have high risks of ineligibility for the PACIFIC trial after CRT.

Our study had several limitations. First, because this was a retrospective study in a single center, information bias was inevitable and sample size was small. Second, our cohort mainly consisted of patients who received consolidation chemotherapy after CRT. Third, owing to the retrospective study design, we had to subjectively modify the inclusion and exclusion criteria used in the PACIFIC trial to some extent.

In conclusion, our study revealed the clinical characteristics and prognoses of patients who became ineligible for the PACIFIC trial after CRT. Physicians should be careful while prescribing CRT for patients with characteristics such as old age, male gender, and radiation therapy with V20 ≥ 35%. Further study is needed for improving the treatment that is provided to these ineligible patients.

Acknowledgements The authors thank Keiko Sakuragawa for her administrative assistance.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest Dr. Hosoya, Dr. Fujimoto, Dr. Kogo, Dr. Kokubo and Dr. Tomii received lecture fees from AstraZeneca K.K. (Tokyo, Japan). Dr. Fujimoto and Dr. Kogo received research funding from AstraZeneca K.K. (Tokyo, Japan) for separate studies. All remaining authors have no conflicts of interest to declare.

Ethical approval All study procedures complied with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

References

1. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67:7–30. https://doi.org/10.3322/caac.21387
2. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C (2012) Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 62:220–241. https://doi.org/10.3322/caac.21149
3. Morgensztern D, Ng S, Gao F, Govindan R (2010) Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. J Thorac Oncol 5:29–33
4. Yoon SM, Shaikh T, Hallman M (2017) Therapeutic management options for stage III non-small cell lung cancer. World J Clin Oncol 8:1–20. https://doi.org/10.5306/wjco.v8.i1.1
5. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC (2017) Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 377:1919–1929. https://doi.org/10.1056/NEJMoa1709937
6. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, de Wit M, Cho BC (2018) Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. https://doi.org/10.1056/nejmoa1809697
7. Vardy J, Dadasovich R, Beale P, Boyer M, Clarke SJ (2009) Eligibility of patients with advanced non-small cell lung cancer for phase III chemotherapy trials. BMC Cancer 9:130
8. Baggstrom MQ, Waqar SN, Sezhiyan AK, Gilstrap E, Gao F, Morgensztern D, Govindan R (2011) Barriers to enrollment in

non-small cell lung cancer therapeutic clinical trials. J Thorac Oncol 6:98–102
9. Al-Baimani K, Jonker H, Zhang T, Goss GD, Laurie SA, Nicholas G, Wheatley-Price P (2018) Are clinical trial eligibility criteria an accurate reflection of a real-world population of advanced non-small-cell lung cancer patients? Curr Oncol 25:e291
10. Kawachi H, Fujimoto D, Morimoto T, Ito M, Teraoka S, Sato Y, Nagata K, Nakagawa A, Otsuka K, Tomii K (2018) Clinical characteristics and prognosis of patients with advanced non-small cell lung cancer who are ineligible for clinical trials. Clin Lung Cancer. https://doi.org/10.1016/j.cllc.2018.05.014
11. Yamamoto N, Nakagawa K, Nishimura Y, Tsujino K, Satouchi M, Kudo S, Hida T, Kawahara M, Takeda K, Katakami N, Sawa T (2010) 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 28:3739–3745. https://doi.org/10.1200/JCO.2009.24.5050
12. Carter DL, Garfield D, Hathorn J, Mundis R, Boehm KA, Ilegbodu D, Asmar L, Reynolds C (2012) A randomized phase III trial of combined paclitaxel, carboplatin, and radiation therapy followed by weekly paclitaxel or observation for patients with locally advanced inoperable non-small-cell lung cancer. Clin Lung Cancer 13:205–213. https://doi.org/10.1016/j.cllc.2011.10.005
13. Senan S, Brade A, Wang LH, Vansteenkiste J, Dakhil S, Biesma B, Martinez Aguillo M, Aerts J, Govindan R, Rubio-Viqueira B, Lewanski C (2016) PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide–cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 34:953–962. https://doi.org/10.1200/JCO.2015.64.8824
14. Steuer CE, Behera M, Ernani V, Higgins KA, Saba NF, Shin DM, Pakkala S, Pillai RN, Owonikoko TK, Curran WJ, Belani CP (2017) Comparison of concurrent use of thoracic radiation with either carboplatin–paclitaxel or cisplatin–etoposide for patients with stage III non-small-cell lung cancer. JAMA Oncol 3:1120. https://doi.org/10.1001/jamaoncol.2016.4280
15. Bowden JCS, Williams LJ, Simms A, Price A, Campbell S, Fallon MT, Fearon KCH (2017) Prediction of 90 day and overall survival after chemoradiotherapy for lung cancer: role of performance status and body composition. Clin Oncol 29:576–584. https://doi.org/10.1016/j.clon.2017.06.005
16. Sanders K, Hendriks LE, Troost E, Bootsma GP, Houben R, Schols A, Dingemans AMC (2016) Early weight loss during chemoradiotherapy has a detrimental impact on outcome in NSCLC. J Thorac Oncol 11:873–879. https://doi.org/10.1016/j.jtho.2016.02.013
17. Topkan E, Parlak C, Selek U (2013) Impact of weight change during the course of concurrent chemoradiation therapy on outcomes in stage IIIB non-small cell lung cancer patients: retrospective analysis of 425 patients. Int J Radiat Oncol Biol Phys 87:697–704
18. Deek MP, Kim S, Ahmed I, Fang BS, Zou W, Malhotra J, Aisner J, Jabbour SK (2016) Prognostic impact of missed chemotherapy doses during chemoradiation therapy for non-small cell lung cancer. Am J Clin Oncol. https://doi.org/10.1097/coc.0000000000000293
19. Shi A, Zhu G, Wu H, Yu R, Li F, Xu B (2010) Analysis of clinical and dosimetric factors associated with severe acute radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with concurrent chemotherapy and intensity-modulated radiotherapy. Radiat Oncol 5:35. https://doi.org/10.1186/1748-717X-5-35
20. Palma DA, Senan S, Tsujino K, Barriger RB, Rengan R, Moreno M, Bradley JD, Kim TH, Ramella S, Marks LB, De Petris L (2013) Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys 85:444–450. https://doi.org/10.1016/j.ijrobp.2012.04.043
21. Zhao Y, Chen L, Zhang S, Wu Q, Jiang X, Zhu H, Wang J, Li Z, Xu Y, Zhang YJ, Bai S (2015) Predictive factors for acute radiation pneumonitis in postoperative intensity modulated radiation therapy and volumetric modulated arc therapy of esophageal cancer. Thorac Cancer 6:49–57. https://doi.org/10.1111/1759-7714.12142
22. National Comprehensive Cancer Network (2019) Non-small cell lung cancer (Version 3.2019). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 16 Feb 2019