Multidisciplinary team discussion results in survival benefit for patients with stage III non-small-cell lung cancer

Hsiu-Ying Hung\textsuperscript{1*}, Yen-Han Tseng\textsuperscript{2,3\#}, Heng-Sheng Chao\textsuperscript{2,3}, Chao-Hua Chiu\textsuperscript{2,3}, Wen-Hu Hsu\textsuperscript{3,4}, Han-Shui Hsu\textsuperscript{3,4}, Yu-Chung Wu\textsuperscript{3,4}, Teh-Ying Chou\textsuperscript{3,5}, Chun-Ku Chen\textsuperscript{3,6}, Keng-Li Lan\textsuperscript{3,7}, Yi-Wei Chen\textsuperscript{3,7}, Yuan-Hung Wu\textsuperscript{3,7}, Yuh-Min Chen\textsuperscript{2,3,8*}

\textsuperscript{1} Nursing Department, Taipei Veterans General Hospital, Taipei, Taiwan, \textsuperscript{2} Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China (R.O.C), \textsuperscript{3} School of Medicine, National Yang-Ming University, Taipei, Taiwan, R.O.C, \textsuperscript{4} Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, R.O.C, \textsuperscript{5} Division of Molecular Pathology, Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, R.O.C, \textsuperscript{6} Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, R.O.C, \textsuperscript{7} Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, \textsuperscript{8} Taipei Cancer Center, Taipei Medical University, Taipei, Taiwan, R.O.C

\# These authors contributed equally to this work.

\* ymchen@vghtpe.gov.tw

Abstract

Background

The treatment for stage III non-small-cell lung cancer (NSCLC) often involves multi-modality treatment. This retrospective study aimed to evaluate whether multidisciplinary team (MDT) discussion results in better patient survival.

Materials and methods

MDT discussion was optional before February 2016 and was actively encouraged by the MDT committee beginning February 2016. We reviewed the medical charts and computer records of patients with stage III NSCLC between January 2013 and December 2018.

Results

A total of 515 patients were included. The median survival of all the patients was 33.9 months (M). The median survival of patients who were treated after MDT discussion was 41.2 M and that of patients treated without MDT discussion was 25.7 M (p = 0.018). The median survival of patients treated before February 2016 was 25.7 M and that of patients treated after February 2016 was 33.9 M (p = 0.003). The median survival of patients with stage IIIA tumors and those with stage IIIB tumors was 39.4 M and 25.7 M, respectively (p = 0.141). Multivariate analysis showed that MDT or not (p<0.001), T staging (p = 0.009), performance status (p<0.001), and surgery (p = 0.016) to be significant prognostic factors.
Conclusion

The results of the study show that MDT discussion results in survival benefit in patients with stage III NSCLC. The MDT discussion, performance status, and if surgery was performed were independent prognostic factors for patients with stage III NSCLC.

Introduction

Stage III non-small cell lung cancer (NSCLC) is a heterogeneous disease. It ranges from T1-T4, N0-N3, and resectable to unresectable. As a result, treatment can vary widely from patient to patient. The treatment options include resection, neoadjuvant chemotherapy, adjuvant chemotherapy, concurrent chemo-radiotherapy (CCRT), and immunotherapy [1, 2]. Previous studies have proven CCRT to be superior to sequential chemoradiation therapy [3, 4]. Currently, definitive CCRT is considered standard of care for patients with stage IIIB NSCLC [5]. There is some controversy regarding the treatment paradigm for stage IIIA patients and thus the importance of multidisciplinary discussion. Treatment of lung cancer has progressed substantially in recent years, including targeted therapy and immunotherapy [6, 7]. The PACIFIC trial concluded CCRT followed by immunotherapy improved outcomes for patients with unresectable stage III NSCLC [8]. In addition, several trials that incorporate immunotherapy into neoadjuvant CCRT are ongoing at the time of this study [9]. ADJUVANT/CTONG1104 found gefitinib to be superior to cisplatin plus vinorelbine as adjuvant treatment for operable non-small cell lung cancer [10]. However, the best treatment strategy for stage III NSCLC has not been determined. Because of this, physicians and other specialists typically have discussions on a case-by-case basis to decide the best strategy for patients with stage III NSCLC. Decisions for the best strategy are based on findings from previous studies, as well as consideration for all available treatment options.

A multidisciplinary team (MDT) is a group of experts that aim to improve the treatment, quality of life, and outcomes for each patient. The concept began in 1970 when a group of specialists met to discuss their patient; this specific format came to be known as a tumor board [11]. MDT discussions offer many advantages, such as more precise diagnosis, shorter time from diagnosis to treatment, increased likelihood of administering all treatments, improved communication from all MDT members, and greater support when management must deviate from guidelines. On the other hand, there are also disadvantages, such as potential delay diagnosis of some patients, inadequate information to facilitate discussion, conflicts of opinions from MDT members, and time required for appropriate meeting preparation [12]. In addition, in studies MDT discussion has improved the quality of life to a greater extent than palliative care [13]. Some studies have suggested MDT discussion may be beneficial for patients with unresectable lung cancer [14, 15]. However, few studies to date have evaluated the benefit of MDT discussion for patients with stage III lung cancer.

Therefore, the aim of the study was to prove MDT discussion could prolong the average time of survival for patients with stage III NSCLC.

Materials and methods

Study design and patients

The thoracic oncology MDT of Taipei Veterans General Hospital began holding MDT meeting from December of 2006. The members of thoracic oncology MDT included chest
physicians, surgeons, medical oncologists, radiation oncologists, radiologists, nuclear medicine physicians, pathologists, nurses, psychologists, and dietitians. All the specialists met once a week to discuss cases of lung cancer, especially in patients whose condition were complicated or in those with stage III tumor. Any case was allowed to be discussed at any point during the course of treatment; examples of case scenarios include when it was difficult to make a diagnosis before treatment, when multiple treatment modalities were indicated during treatment, and when it was too difficult to evaluate the response after treatment. At the hospital of focus, MDT discussion was initiated by doctors in charge of the patients on an option basis before February 2016 and is was actively encouraged by MDT committee for stage III NSCLC patients beginning February 2016.

We retrospectively reviewed chart and computer record of stage III NSCLC patients from January 2013 to December 2018. The clinicopathological data were recorded, including age, gender, smoking status, Eastern Cooperative Oncology Group performance status (ECOG PS), clinical staging (T status, and N status), and histology. We also recorded whether or not the patients underwent surgical intervention. All data were fully anonymized before we initially access them. The study was approved by the Institutional Ethical Review Board of Taipei Veterans General Hospital (VGHIRB No.: 2019-07-056BC) and informed consent was not required according to our institutional guidelines.

Efficacy evaluation

Chest computed tomography scan was performed 1 month before treatment for staging and every 2 to 3 months after treatment in order to confirm the treatment response. The World Health Organization (WHO) TNM staging version 7 was used in this study [16]. Types of responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [17]. Overall survival was measured from the date of initiation of first treatment to the date of death due to any cause or the last follow-up. Overall survival was censored for the patients who were still alive at the time of the last follow-up visit.

Statistical analysis

All categorical variables were analyzed with 2 tests. Mann-Whitney U test were used for continuous variables when comparing 2 groups. Median overall survival (OS) were calculated using the Kaplan-Meier method and compared by log-rank test. Cox-regression analysis was used for multivariate OS analysis. All statistical analyses were performed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA).

Results

Patients

A total of 515 patients with stage III tumors were included in this study, of which 348 were men and 167 were women. The mean age was 68 years old, which ages ranging from 20 to 95 years old. The median follow up time was 34.30 months for patients received MDT and 23.83 months for patients who did not receive MDT. MDT discussion was performed for 39.4% of patients with stage III NSCLC between January 2013 and January 2016, and that increased to 69.3% of patients between February 2016 and December 2018 (p<0.001). The median length of survival of all the patients was 33.9 months (95% confidence interval [CI] 27.1–40.7). The median length of survival of patients who received treatment after MDT discussion (n = 235) was 41.2 months, as compared to 25.7 months for patients who received treatment without MDT discussion (n = 280; 95% CI 23–59.4, 17.1–34.3; p = 0.018, Fig 1). The median survival
of all the patients treated before February 2016 was 25.7 months (n = 296, 95% CI 17.6–33.8), which increased to 33.9 months for patients treated after February 2016 (n = 219, 95% CI 27.1–40.7; p = 0.003, Fig 2). The median length of survival of male and female patients was 24.7 months (n = 348, 95% CI 19.7–29.7) and 53.4 months (n = 167, 95% CI —), respectively (p<0.001). The median survival of never smokers and smokers was not reached (n = 201, 95% CI —) and 21.2 months (n = 314, 95% CI 17.2–25.2), respectively (p<0.001). The median length of survival according to the PS was not reached (95% CI —) for patients with a PS score of 0 (n = 206), 24.9 months (95% CI 18.4–31.4) for patients with a PS score of 1 (n = 244), 8.6 months (95% CI 1.7–15.5) for those with a PS score of 2 (n = 42), 3.7 months (95% CI 2.1–5.3) for those with a PS score of 3 (n = 17), and 2.9 months (95% CI 0–6.3) for those with a PS score of 4 (n = 6; p<0.001). The median length of survival for patients with squamous cell carcinoma (n = 184), adenocarcinoma (n = 281), and other subtypes (n = 50) was 17.8 months.
(95% CI 15.6–20), 58.5 months (95% CI 38.6–78.4), and 21.3 months (95% CI 13.3–29.3), respectively (p < 0.001). The median length of survival of patients with stage IIIA tumors (n = 276) and those with stage IIIB tumors (n = 239) was 39.4 months (95% CI 28.9–49.9) and 25.7 months (95% CI 15.9–35.5), respectively (p = 0.141). The median survival of patients who underwent surgery (n = 148) and those who did not was not reached (95% CI —) and 24 months (n = 367, 95% CI 19.7–28.3), respectively (p < 0.001).

**Survival according to different TNM stages**

Filtering data according to T status, the median survival for patients was not reached (95% CI —) in patients with T1 disease (n = 57), 39.6 months (95% CI —) in those with T2 disease (n = 146), 21.2 months (95% CI 16.8–25.6) in those with T3 disease (n = 159), and 26.4 months (95% CI 11.4–41.4) in patients with T4 disease (n = 153; p = 0.001). Filtering data according to N status, the median length of survival for patients with N0 disease (n = 32) was not reached.
(95% CI — ), in patients with N1 disease (n = 67) was 26.8 months (95% CI 19–34.6), in patients with N2 disease (n = 246) was 37.6 months (95% CI 28.8–46.4), and in patients with N3 disease (n = 170) was 25.7 months (95% CI 13.2–38.2).

**Cox regression model analysis for all the factors**

Multivariate analysis included whether or not MDT discussion was performed, sex, staging, T status, and N status, smoking, PS, histology, and whether surgery was performed. The results showed that MDT or not (p<0.001), T staging (p = 0.009), ECOG PS (p<0.001), and surgery (p = 0.016) were significant prognostic factors (Table 1). According to the result of multivariate analysis, MDT discussion prolonged length of survival of patients with stage III lung cancer.

**Discussion and conclusion**

The current study is to demonstrate MDT discussion prolongs the survival time of patients with stage III NSCLC. In fact, previous studies have shown poor outcomes for patients with stage III NSCLC. The 5 year survival rate is approximately 15–30% [2, 18]. Although some clinical trials have used consolidation chemotherapy after standard CCRT, they have still failed

| Table 1. General data for patients from 2013 to 2018. |
|---------------------------------|----------|-----------------|--------------------|-----------------|-----------------|
| Before Feb 2016 vs later         | Patient number | Median survival (months) | 95% CI          | p value  | Cox regression |
| Before Feb 2016 vs later         | before       | 25.7             | 17.6–33.8         | 0.003   | N/A            |
| After Feb 2016 vs later          | after        | 33.9             | 27.1–40.7         | 0.018   | 0.184          |
| MTD vs no MTD                    | yes          | 39.6             | 23–56.2           | 0.141   | 0.795          |
| MTD vs no MTD                    | no           | 25.7             | 27.1–40.7         |         |                |
| Gender                           | male         | 24.7             | 19.7–29.7         | 0.000   | 0.205          |
| Gender                           | female       | 53.4             | NR                |         |                |
| Staging                          | IIIA         | 39.4             | 28.9–49.9         |         |                |
| Staging                          | IIIB         | 25.7             | 15.9–35.5         |         |                |
| Staging                          | III          | 33.9             | 27.1–40.7         |         |                |
| T                                | 1            | 57               | NR                | 0.001   | 0.008          |
| T                                | 2            | 146              | 39.6              | 0.141   | 0.795          |
| T                                | 3            | 159              | 21.2              | 0.000   | 0.205          |
| T                                | 4            | 153              | 26.4              | 0.141   | 0.795          |
| N                                | 0            | 32               | NR                | 0.928   | 0.131          |
| N                                | 1            | 67               | 26.8              | 0.000   | 0.000          |
| N                                | 2            | 246              | 37.6              | 0.000   | 0.000          |
| N                                | 3            | 170              | 25.7              | 0.000   | 0.000          |
| N                                | 4            | 170              | 25.7              | 0.000   | 0.000          |
| smoking                          | no           | 201              | NR                | 0.000   | 0.000          |
| smoking                          | yes          | 314              | 21.2              | 0.000   | 0.000          |
| ECOG PS                          | 0            | 206              | NR                | 0.000   | 0.000          |
| ECOG PS                          | 1            | 244              | 24.9              | 18.4–31.4 |                 |
| ECOG PS                          | 2            | 42               | 8.6               | 1.7–15.5 |                 |
| ECOG PS                          | 3            | 17               | 3.7               | 2.1–5.3 |                 |
| ECOG PS                          | 4            | 6                | 2.9               | 0–6.3 |                 |
| surgery                          | yes          | 148              | NR                | 0.000   | 0.023          |
| surgery                          | no           | 367              | 24                | 19.7–28.3 |                 |

MDT: multi-disciplinary team; PS: performance status; NR: not reached.

https://doi.org/10.1371/journal.pone.0236503.t001
to prolong the PFS [19, 20]. In previous studies, the median length of survival was 18–23 months [21, 22]. In our study, the median length of survival was 25.7 months in patients who received treatment without MDT discussion, and this result was similar to the length of survival obtained in previous studies. However, the median length of survival time in our study was 41.2 months when patients received treatment after MDT discussion. This result suggests that MDT prolongs the length of survival for patients with stage III NSCLC. In addition, the median length of survival is approximately 22–24 months for patients with stage IIIA disease and 12–15 months for patients with stage IIIB disease [23–26]. The current study found the median survival was 39.4 months for patients with stage IIIA disease and 25.7 months for patients with stage IIIB disease. Thus, the median length of survival was longer for patients included in the current study than for patients in previous studies. The recently PACIFIC trial is among the most commonly cited studies that enrolled patients with stage III, unresectable NSCLC. The median length of survival of patients in the placebo group in PACIFIC trial was 16.2 months [8]. Meanwhile, the median length of survival of patients who did not undergo surgery was 24 months. Thus, MDT discussion seems to play a key role in prolonging the survival of patients with stage III NSCLC.

MDT discussion began in our hospital in 2007. MDT discussion was performed for only 39.4% of patients with stage III NSCLC patients between January 2013 and January 2016. In 2015, Kehl KL et al. concluded that MDT should focus on complex cases because combined modality treatment are more likely to provide benefit for lung cancer patients [27]. In the current study, MDT discussion was performed for patients with stage III NSCLC; 69.3% of patients with stage III lung cancer were treated after MDT discussion between February 2016 and December 2018. The median length of survival of all the patients treated before February 2016 was 25.7 months (n = 296, 95% C.I. 17.6–33.8), and it increased to 33.9 months for patients treated after February 2016 (n = 219, 95% C.I. 27.1–40.7) (p = 0.003).

The findings of the current study showed that the survival of female patients was better than that of male patients. The influence of sex on survival of patients with NSCLC is still unclear and results are inconclusive. While some studies have concluded that sex may not affect the survival of patients with resectable NSCLC [28, 29], others have shown male gender to be an unfavorable prognostic factor for non-small cell lung cancers [30, 31]. But, the reason for the difference in results is not clear. Pinto et al. indicated female patients may benefit more from targeted therapy. In addition, more male patients are smokers than female patients [32]. In the current study we did not check EGFR status for every patient. Therefore more data are warranted in order to make a conclusion.

In the current study, never smokers had a longer survival than smokers. Smoking increases not only the risk of lung cancer but also the rate of recurrence [33]. Moreover, smoking appears to decrease the response to cancer treatment [34–36]. Continuing smoking after diagnosis of lung cancer is known to increase the risk all-cause mortality for patients [33]. Therefore, smoking cessation is necessary for effective lung cancer treatment [37–39]. We recommend MDT discussion should also include a program for smoking cessation as a part of lung cancer care.

In previous studies PS has been associated with length of survival for patients with NSCLC [40, 41]. It is known that PS would influence a physician’s decision regarding the appropriateness of chemotherapy [42]. Data in the current study revealed patients with better PS had longer length survival. In addition, MDT discussion did not result in a more aggressive treatment plan. In our study, 23 patients had a PS score of 3–4, and most of them received supportive care or palliative radiotherapy regardless of whether or not there were MDT discussions.

TNM staging is the most important predictor for length of survival for patients with lung cancer. IASLC published the AJCC 7 staging manual and its results showed the median length
of survival was not reached, 113 months, 81 months, 56 months, and 29 months when the tumor size was <2 cm (T1a), 2–3 cm (T1b), 3–5 cm (T2a), 5–7 cm (T2b), and >7 cm (T3), respectively, among patients with stage I-IV NSCLC [43]. In the current study, the median length of survival was not reached for patients with T1 disease, 39.6 months for those with T2 disease, 21.2 months for those with T3 disease, and 26.4 months for those with T4 disease. Thus, the survival of patients with the same T stage was still worse for patients with stage III NSCLC.

There are some limitations about this study that should be mentioned. First, this was a retrospective study, so there was undoubtedly some selection bias. A large, prospective, randomized trial is necessary to achieve definite answers to the questions raised. Second, Due to differences in patient characteristics, physicians might choose different chemotherapy regimens, which could confound the outcome of the study. Finally, treatment options increase and guidelines change as time goes by. These factors could influence outcomes of patients with lung cancer.

In conclusion, MDT discussion is essential given current treatment options and efforts to maximize effectiveness. Although treatment for patients with stage III NSCLC is complicated, MDT discussion prolongs their survival time and should be actively performed.

Supporting information
S1 Raw Data.
(XLSX)

Author Contributions
Conceptualization: Yuh-Min Chen.
Data curation: Hsiu-Ying Hung, Yen-Han Tseng, Chao-Hua Chiu, Wen-Hu Hsu, Han-Shui Hsu, Yu-Chung Wu, Teh-Ying Chou, Chun-Ku Chen, Keng-Li Lan, Yi-Wei Chen, Yuan-Hung Wu.
Formal analysis: Hsiu-Ying Hung, Yen-Han Tseng, Han-Shui Hsu, Yu-Chung Wu, Teh-Ying Chou, Chun-Ku Chen, Keng-Li Lan, Yi-Wei Chen, Yuh-Min Chen.
Investigation: Heng-Sheng Chao, Yuan-Hung Wu, Yuh-Min Chen.
Methodology: Heng-Sheng Chao, Chao-Hua Chiu, Yuh-Min Chen.
Project administration: Yuh-Min Chen.
Supervision: Wen-Hu Hsu.
Writing – original draft: Yen-Han Tseng.
Writing – review & editing: Yuh-Min Chen.

References
1. Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC, Balekian AA, et al. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013; 143(5 Suppl):e314S–e40S. https://doi.org/10.1378/chest.12-2960 PMID: 23649445.
2. Yoon SM, Shaikh T, Hallman M. Therapeutic management options for stage III non-small cell lung cancer. World journal of clinical oncology. 2017; 8(1):1–20. https://doi.org/10.5306/wjco.v8.i1.1 PMID: 28246582; PubMed Central PMCID: PMC5309711.
3. Curran WJ Jr., Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. Journal of
the National Cancer Institute. 2011; 103(19):1452–60. https://doi.org/10.1093/jnci/djr325 PMID: 21903745; PubMed Central PMCID: PMC3186782.

4. Furuse K, Fukuoaka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1999; 17(9):2692–9. https://doi.org/10.1200/JCO.1999.17.9.2692 PMID: 10561343.

5. Watanabe SI, Nakagawa K, Suzuki K, Takamochi K, Ito H, Okami J, et al. Neoadjuvant and adjuvant therapy for Stage III non-small cell lung cancer. Japanese journal of clinical oncology. 2017; 47(12):1112–8. https://doi.org/10.1093/jjco/hyx147 PMID: 29136212.

6. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. The New England journal of medicine. 2018; 378(22):2078–92. https://doi.org/10.1056/NEJMoa1801005 PMID: 29658856.

7. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. The New England journal of medicine. 2018; 378(2):113–25. https://doi.org/10.1056/NEJMoa1713137 PMID: 29151359.

8. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. The New England journal of medicine. 2017; 377(20):1919–29. https://doi.org/10.1056/NEJMoa1709937 PMID: 2888581.

9. Lewis J, Gillaspie EA, Osmundson EC, Horn L. Before or After: Evolving Neoadjuvant Approaches to Locally Advanced Non-Small Cell Lung Cancer. Frontiers in oncology. 2018; 8:5. https://doi.org/10.3389/fonc.2018.00005 PMID: 29410947; PubMed Central PMCID: PMC5787144.

10. Zhong WZ, Wang Q, Mao WM, Xu ST, Wu L, Shen Y, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. The Lancet Oncology. 2018; 19(1):139–48. https://doi.org/10.1016/S1470-2045(17)30729-5 PMID: 29174310.

11. Gross GE. The role of the tumor board in a community hospital. CA: a cancer journal for clinicians. 1987; 37(2):88–92. https://doi.org/10.3322/canjclin.37.2.88 PMID: 3102006.

12. Powell HA, Baldwin DR. Multidisciplinary team management in thoracic oncology: more than just a concept? The European respiratory journal. 2014; 43(6):1776–86. https://doi.org/10.1183/09031936.00150813 PMID: 24525445.

13. Boxer MM, Vinod SK, Shafig J, Duggan KJ. Do multidisciplinary team meetings make a difference in the management of lung cancer? Cancer. 2011; 117(22):5112–20. https://doi.org/10.1002/cncr.26149 PMID: 21523766.

14. Forrest LM, McMillan DC, McArdle CS, Dunlop DJ. An evaluation of the impact of a multidisciplinary team, in a single centre, on treatment and survival in patients with inoperable non-small-cell lung cancer. British journal of cancer. 2005; 93(9):977–8. https://doi.org/10.1038/sj.bjc.6602825 PMID: 16234818; PubMed Central PMCID: PMC2361678.

15. Bydder S, Nowak A, Marion K, Phillips M, Atun R. The impact of case discussion at a multidisciplinary team meeting on the treatment and survival of patients with inoperable non-small cell lung cancer. International medicine journal. 2009; 39(12):838–41. https://doi.org/10.1111/j.1445-5994.2009.02019.x PMID: 20233244.

16. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of surgical oncology. 2010; 17(6):1471–4. https://doi.org/10.1245/s10434-010-0985-4 PMID: 20180029.

17. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009; 45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026 PMID: 19097774.

18. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. The Lancet Oncology. 2015; 16(2):187–99. https://doi.org/10.1016/S1470-2045(14)71207-0 PMID: 25601342; PubMed Central PMCID: PMC4419359.

19. Ahn JS, Ahn YC, Kim JH, Lee CG, Cho EK, Lee KC, et al. Multinational Randomized Phase III Trial With or Without Consolidation Chemotherapy Using Docetaxel and Cisplatin After Concurrent Chemoradiation in Inoperable Stage III Non-Small-Cell Lung Cancer: KCSG-LU05-04. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2015; 33(24):2660–6. https://doi.org/10.1200/JCO.2014.60.0130 PMID: 26150444.

20. Tsujino K, Kurata T, Yamamoto S, Kawaguchi T, Kubo A, Isa S, et al. Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer?
MDT improved survival of stage III lung cancer

cancer? A pooled analysis of the literature. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2013; 8(8):1181–9. https://doi.org/10.1097/JTO.0b013e3182988348 PMID: 23883782.

21. Kelly K, Chansky K, Gaspar LE, Albain KS, Jett J, Ung YC, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2008; 26(15):2450–6. https://doi.org/10.1200/JCO.2007.14.4824 PMID: 18378568.

22. Hanna N, Neubauer M, Yiannoutsos C, McGarry R, Arseneau J, Ansari R, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology https://doi.org/10.1200/JCO.2008.17.7840 PMID: 19001323 Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2008; 26(35):5755–60.

23. Urvay SE, Yucel B, Erdis E, Turan N. Prognostic Factors in Stage III Non-Small-Cell Lung Cancer Patients. Asian Pacific journal of cancer prevention: APJCP. 2016; 17(10):4693–7. https://doi.org/10.22034/apjcp.2016.17.10.4693 PMID: 27893199; PubMed Central PMCID: PMC5454619.

24. Ozkaya S, Fındık S, Dirican A, Atilci AG. Long-term survival rates of patients with stage IIIb and IV non-small cell lung cancer treated with cisplatin plus vinorelbine or gemcitabine. Experimental and therapeutic medicine. 2012; 4(6):1035–8. https://doi.org/10.3892/etm.2012.714 PMID: 23226770; PubMed Central PMCID: PMC3494120.

25. Ryan KJ, Skinner KE, Fernandes AW, Pavilack M, Walker MS, et al. Real-world outcomes in patients with unresected stage III non-small cell lung cancer. Medical oncology. 2019; 36(3):24. https://doi.org/10.1007/s12032-019-1249-1 PMID: 30706218.

26. Kelly SM, Vangel MG, Adak S, Wagner H, Schiller JH, Herskovic A, et al. The influence of gender on survival and tumor recurrence following adjuvant therapy of completely resected stages II and IIia non-small cell lung cancer. Lung cancer. 2002; 37(3):303–9. https://doi.org/10.1016/S0169-5002(02)00103-4 PMID: 12234700.

27. Kehl KL, Landrum MB, Kahn KL, Gray SW, Chen AB, Keating NL. Tumor board participation among physicians caring for patients with lung or colorectal cancer. Journal of oncology practice. 2015; 11(3):e267–78. https://doi.org/10.1200/JOP.2015.003673 PMID: 25922221; PubMed Central PMCID: PMC4381111.

28. Keller SM, Vangel MG, Adak S, Wagner H, Schiller JH, Herskovic A, et al. The influence of gender on survival and tumor recurrence following adjuvant therapy of completely resected stages II and IIia non-small cell lung cancer. Lung cancer. 2002; 37(3):303–9. https://doi.org/10.1016/S0169-5002(02)00103-4 PMID: 12234700.

29. Sakurai H, Asamura H, Goya T, Eguchi K, Nakanishi Y, Sawabata N, et al. Survival differences by gender for resected non-small cell lung cancer: a retrospective analysis of 12,509 cases in a Japanese Lung Cancer Registry study. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2010; 5(10):1594–601. https://doi.org/10.1097/JTO.0b013e3181f1923b PMID: 20736855.

30. Santana-Davila R, Martins R. Treatment of Stage IIIA Non-Small-Cell Lung Cancer: A Concise Review. https://doi.org/10.1097/JCO.2008.17.7840 PMID: 19001323 Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2008; 26(35):5755–60.

31. Visbal AL, Williams BA, Nichols FC, 3rd, Marks RS, Jett JR, Aubry MC, et al. Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. The Annals of thoracic surgery. 2003.11.021 PMID: 15223430.

32. Pinto JA, Vallejos CS, Raez LE, Mas LA, Ruiz R, Torres-Roman JS, et al. Gender and outcomes in non-small cell lung cancer: an old prognostic variable comes back for targeted therapy and immunotherapy? ESMO open. 2018; 3(3):e000344. https://doi.org/10.1136/esmoopen-2018-000344 PMID: 29682532; PubMed Central PMCID: PMC5905840.

33. Parsons A, Daley A, Beigh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. Bmj. 2010; 340:b5569. https://doi.org/10.1136/bmj.b5569 PMID: 20993278; PubMed Central PMCID: PMC2809841.

34. Warren GW, Sobus S, Gritz ER. The biological and clinical effects of smoking by patients with cancer and strategies to implement evidence-based tobacco cessation support. The Lancet Oncology. 2014; 15(12):e565–80. https://doi.org/10.1016/S1470-2045(14)70266-9 PMID: 25438699; PubMed Central PMCID: PMC3977974.

35. Sobus SL, Warren GW. The biologic effects of cigarette smoke on cancer cells. Cancer. 2014; 120(23):3617–26. https://doi.org/10.1002/cncr.28904 PMID: 25043526.
36. Warren GW, Singh AK. Nicotine and lung cancer. Journal of carcinogenesis. 2013; 12:1. https://doi.org/10.4103/1477-3163.106680 PMID: 23599683; PubMed Central PMCID: PMC3622363.

37. Gritz ER, Toll BA, Warren GW. Tobacco use in the oncology setting: advancing clinical practice and research. https://doi.org/10.1158/1055-9965.EPI-13-0896 PMID: 24420982. 2014; 23(1):3–9. PubMed Central PMCID: PMC3893715.

38. Gulati S, Mulshine JL. Lung cancer screening guidelines: common ground and differences. Translational lung cancer research. 2014; 3(3):131–8. https://doi.org/10.3978/j.issn.2218-6751.2014.06.12 PMID: 25806292; PubMed Central PMCID: PMC3893715.

39. Warren GW, Ward KD. Integration of tobacco cessation services into multidisciplinary lung cancer care: rationale, state of the art, and future directions. Translational lung cancer research. 2015; 4(4):339–52. https://doi.org/10.3978/j.issn.2218-6751.2015.07.15 PMID: 26380175; PubMed Central PMCID: PMC4549462.

40. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group Study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1986; 4(5):702–9. https://doi.org/10.1200/JCO.1986.4.5.702 PMID: 3701389.

41. Gebbia V, Galetta D, De Marinis F. Non small cell lung cancer patients with ECOG PS2: unsolved questions and lessons from clinical trials. Annals of oncology: official journal of the European Society for Medical Oncology. 2005; 16 Suppl 4:iv123–31. https://doi.org/10.1093/annonc/mdi921 PMID: 15923412.

42. Salloum RG, Smith TJ, Jensen GA, Lafata JE. Survival among non-small cell lung cancer patients with poor performance status after first line chemotherapy. Lung cancer. 2012; 77(3):545–9. https://doi.org/10.1016/j.lungcan.2012.04.019 PMID: 22633939; PubMed Central PMCID: PMC3423534.

43. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2007; 2(8):706–14. https://doi.org/10.1097/JTO.0b013e31812f3c1a PMID: 17762336.