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ORIGINAL ARTICLE

Results of neoadjuvant chemo(radio)therapy and resection for stage IIIA non-small cell lung cancer in The Netherlands

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ABSTRACT

Introduction: Concurrent chemoradiotherapy remains the main treatment strategy for patients with stage IIIA non-small cell lung cancer (NSCLC); stage cT3N1 or cT4N0-1 may be eligible for surgery and potentially resectable stage IIIA (N2) NSCLC for neoadjuvant therapy followed by resection. We evaluated treatment patterns and outcomes of patients with stage IIIA NSCLC in The Netherlands.

Material and Methods: Primary treatment data of patients with clinically staged IIIA NSCLC between 2010 and 2016 were extracted from The Netherlands Cancer Registry. Patient characteristics were tabulated and 5-year overall survival (OS) was calculated and reported.

Results: In total, 9,591 patients were diagnosed with stage IIIA NSCLC. Of these patients, 41.3% were treated with chemoradiotherapy, 11.6% by upfront surgery and 428 patients (4.5%) received neoadjuvant treatment followed by resection. The 5-year OS was 26% after chemoradiotherapy, 40% after upfront surgery and 54% after neoadjuvant treatment followed by resection. Clinical over staging was seen in 42.3% of the patients that were operated without neoadjuvant therapy.

Conclusion: In The Netherlands, between 2010 and 2016, 4.5% of patients with stage IIIA NSCLC were selected for treatment with neoadjuvant therapy followed by resection. The 5-year OS in these patients exceeded 50%. However, the outcome might be overestimated due to clinical over staging.

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Introduction

In The Netherlands, lung cancer is diagnosed in approximately 13,000 patients annually, with 87% of cases being non-small cell lung cancer (NSCLC) [1]. Of these patients, around 14% are diagnosed with clinical stage IIIA [2]. Stage IIIA NSCLC comprises a heterogeneous group of patients and standard treatment includes multiple modalities [3,4]. Concurrent CRT remains the main treatment strategy for stage IIIA NSCLC. However, stage cT3N1 may be eligible for upfront surgery and for potentially resectable stage IIIA (N2) NSCLC, neoadjuvant therapy followed by resection is recommended as an alternative [3,4]. A phase III randomized trial with patients included between 1994 and 2001 did not demonstrate a survival difference between CRT and CRT followed by a resection (trimodality treatment; TT) [5]. However, subgroup analysis suggested better progression-free survival (PFS) and overall survival (OS) after TT for selected patients with single-level N2 disease and mediastinal downstaging after CRT, who were eligible for lobectomy [5,6]. Diagnostic work-up and treatment options evolved considerably after 2001, including the introduction of the fluorodeoxyglucose positron-emission tomography (FDG-PET) scan, endobronchial ultrasound (EBUS), transesophageal ultrasound (EUS), the staging of brain metastasis with magnetic resonance imaging (MRI) scan, the introduction of intensity-modulated – and image-guided radiotherapy and the introduction of thoracoscopic and robotic surgery. Treatment choice and surgical results may also rely on hospital experience and case volume [7]. In The Netherlands, a reduction in the number of hospitals with in-house pulmonary surgery was effectuated from 78 in 2005 to 43 in 2015 [8,9], which had resulted in performing more pulmonary resections per hospital per year. The aim of this study was to evaluate current treatment patterns and outcomes for patients with clinical stage IIIA NSCLC in The Netherlands with a focus on contemporary results of neoadjuvant therapy and resection, using population-based data.

Material and methods

Data from patients with clinical stage IIIA NSCLC diagnosed from 2010 till 2016 were retrieved from The Netherlands Cancer Registry (NCR), after formal approval by the NCR Monitoring Committee. The NCR collects data of all cancer patients diagnosed in The Netherlands. It is notified of newly

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diagnosed malignancies by the national automated pathological archive and of hospital discharge diagnoses. Information on demographics, diagnosis, staging, and treatment is extracted from medical records in all 78 Dutch hospitals by NCR personnel. Considering its retrospective and non-interventional nature, this study does not require approval from an accredited medical ethics committee (MEC) or the Central Committee on Research involving Human Subjects (CCMO). Stage information was recorded according to the 7th edition of the Union for International Cancer Control (UICC) TNM classification [7]. Survival status was updated annually *via* a computerized link with the national civil registry. Information on death certificates or cause of death is not available. Data on comorbidity or performance status is not available. Patients treated abroad ($n = 16$) were excluded from the analysis. TNM 7 stage was regrouped into 4 categories, T1–2 N2, T3 N1, T3 N2 and T4 N0–1. Patients with stage Tx N1 ($n = 53$) were added to the T3 N1 category. Patients with stage T0 N2 ($n = 76$) or Tx N2 ($n = 351$) were added to the T1–2 N2 category. Staging may have been suboptimal in patients who were not considered fit enough for active treatment. Guideline recommended staging procedures for stage III in The Netherlands comprise computed tomography (CT) scan and FDG-PET scan and MRI or CT scan of the brain and minimally invasive staging by EBUS/EUS or mediastinoscopy. The database contained information on pathological verification of lymph node metastases but not on the timing of pathological confirmation of N2 involvement. For operated patients, postsurgical TNM information was available. Neoadjuvant treatment before surgery was defined as chemotherapy or CRT and included patients with superior sulcus tumors. Information on concurrent or sequential administration of chemotherapy and fractionation schedules and total dose of radiotherapy was not available, however, the national guideline recommends (chemo)radiation $\geq$60 Gy and this guideline are endorsed by all radiotherapy departments. To examine regional variation in the use of induction surgery, The Netherlands was subdivided into 7 regions, named A to G. Association between the region and the frequency and type of induction treatment was tabulated and tested for significance by chi-square analysis.

Survival time was calculated from the day of diagnosis until the day of death or censoring and was not calculated from the time of treatment start or time of surgery. The Median follow-up of censored cases was 53 months. Variation in survival between stage categories and type of neoadjuvant treatment is graphically shown and tested for significance by the log-rank test. Five-year OS by treatment group was calculated with 95% confidence intervals. Variation in survival between treatment groups was not tested for significance due to major disparities in patient and tumor characteristics that could not be resolved by multivariable analysis. Kaplan Meier estimates were calculated from the date of lung cancer diagnosis until death (censored at last follow-up), stratified by stage subgroups (T1–2 N2, T3 N1, T3 N2 and T4 N0–1). Statistical analyses were performed using the STATA software package, version 14 (Stata Corp, College Station, TX).

Results

Between 2010 and 2016, 9591 patients were diagnosed with stage IIIA NSCLC stage. Of these, 6042 patients (63%) were male and 3549 (37%) were female. Half of the patients were 70 years or older (Table 1). Treatment analysis revealed that 3962 patients (41.3%) received definitive CRT, 1115 patients (11.6%) underwent primary resection and 428 patients (4.5%) were treated with neoadjuvant therapy followed by resection. After upfront surgery, adjuvant chemotherapy was given in 456/1115 (41%) of patients. A considerable fraction (42.6%) of patients received other treatments, such as radiotherapy only, palliative treatment or best supportive care.

With respect to TNM stage, 4279 patients were clinically staged T1–2 N2, 769 were staged T3 N1, 2023 were staged T3 N2 and 2,520 were staged T4 N0–1. TT was more common in younger patients and those with a clinically staged T3 N1 tumor. In the group of patients with stage T3N1, 40.1% of the patients were treated with upfront surgery without neoadjuvant treatment. Neoadjuvant treatment consisted of CRT in 341 (80%) patients and chemotherapy in 87 (20%). Administration of neoadjuvant therapy followed by a resection varied between regions from 2.9 to 7.3% ($p < 0.001$) (Table 2). In 3 hospitals, neoadjuvant treatment followed by a resection was performed more than 3 times per year.

Positive lymph nodes on FDG-PET were pathologically confirmed in 29% of patients with cN1 disease and 57% of

Table 1. Treatment patterns for patients with clinical stage IIIA NSCLC.

		n (%)	CRT (%)	Upfront surgery (%)	Neoadjuvant therapy + resection (%)	Other (%)
Gender	Men	6042 (63.0)	40.0	11.3	4.6	44.1
	Women	3549 (37.0)	43.5	12.2	4.3	40.0
Age	18–59	1813 (18.9)	56.8	13.8	10.9	18.5
	60–69	3025 (31.5)	50.9	14.7	5.8	28.5
	70–79	3172 (33.1)	38.8	11.9	1.7	47.7
	80+	1581 (16.5)	10.3	2.7	0.1	87.0
Period	2010–2011	2674 (27.9)	43.1	11.2	4.1	41.6
	2012–2013	2798 (29.2)	40.7	11.4	4.0	43.9
	2014–2016	4119 (42.9)	40.5	12.0	5.0	42.4
TNM stage	T1–2 N2	4279 (44.6)	48.9	7.6	3.5	40.0
	T3 N1	769 (8.0)	18.3	40.1	7.2	34.5
	T3 N2	2023 (21.1)	44.4	5.3	5.6	44.6
	T4 N0-1	2520 (26.3)	32.9	14.8	4.3	47.9
Total		9591 (100)	41.3	11.6	4.5	42.6

n: number of patients; CRT: chemoradiotherapy; TNM: 7th edition TNM.

patients with cN2 disease after staging by EBUS/EUS or mediastinoscopy. However, the number of patients who received an FDG-PET scan is unknown. In patients that were operated without any neoadjuvant therapy, pathological examination of the resection specimen revealed a lower TNM stage in 42.3% (Table 3) of the patients. The agreement between clinical and postoperative pathological TNM stage was observed in 53.8%. A lower pTNM stage after upfront surgery was more common in patients with T1–2 N2 disease (49%) or T3 N1 disease (50%) than in patients with T3 N2 (42%) or T4 N0–1 (30%) disease. Downstaging in patients that were treated with neoadjuvant CRT or chemotherapy followed by a resection was observed in 75.9 and 67.8% of patients, respectively (Table 3). Downstaging to a complete pathological response (ypT0 N0) after neoadjuvant treatment was observed in 33% of patients after CRT versus 11% after neoadjuvant chemotherapy.

The 5-year OS was 26% (95% CI 25–28%) after CRT, 40% (95% CI 37–44%) after upfront surgery and 54% (95% CI 49–59%) after neoadjuvant treatment followed by resection. Two- and three-year survival after neoadjuvant treatment and resection were 75% (95% CI 70–78) and 63% (95% CI 58–67), respectively. Categorized according to induction treatment, 5-year OS was 52% after CRT (95% CI 46–57%) and 64% after chemotherapy (95% CI 53–74%). The 5-year OS after upfront surgery was 36% for patients with true pIIIA-disease, versus 47% for patients with < pIIIA and 31% for those > pIIIA.

Surgical resection after neoadjuvant therapy included lobectomy, pneumonectomy, bilobectomy or sublobar resection in 76, 16, 6 and 3% of cases, respectively. Postsurgical 30-day mortality was 4.3% after pneumonectomy or bilobectomy versus 0.9% after lobectomy or sublobar resection, with a 90-day mortality of 9.8 and 4.8%, respectively. After neoadjuvant treatment followed by bilobectomy/pneumonectomy, 5-year OS was 44% (95% CI 33–54%), versus 57% (95% CI 51–62%) for lobectomy or sublobar resection. Figure 1 shows the 5-year OS after neoadjuvant therapy followed by resection for each stage subgroup. The 5-year OS was 52, 53, 51 and 61% in the subgroups T1–2 N2, T3 N1, T3 N2 and T4 N0–1, respectively.

Table 2. Regional variation in the proportion of patients with clinical stage IIIA NSCLC treated with neoadjuvant therapy followed by a resection ($p < 0.001$).

Region in The Netherlands	A	B	C	D	E	F	G
Number of patients	1299	1464	1345	1970	853	940	1720
Chemotherapy (%)	1.5	1.4	0.4	1.4	0.8	0.4	0.2
Chemoradiotherapy (%)	2.3	5.9	2.5	2.7	2.9	2.6	5.1
Total (%)	3.8	7.3	2.9	4.1	3.7	3.0	5.3

Table 3. Postsurgical pathological stage for patients with clinical stage IIIA NSCLC treated by upfront surgery without neoadjuvant therapy or neoadjuvant treatment followed by a resection.

Treatment	*n*	<IIIA (%)	IIIA (%)	>IIIA (%)
Upfront surgery (no neoadjuvant treatment)	1115	42.3	53.8	3.9
Neoadjuvant chemotherapy + resection	87	67.8	32.2	0
Neoadjuvant chemoradiotherapy + resection	341	75.9	22.9	1.2

Discussion

Our population-based data of 9591 patients with stage IIIA NSCLC showed that between 2010 and 2016, only 4.5% of patients with stage IIIA NSCLC were treated with CRT or chemotherapy followed by resection. The 5-year OS in these selected patients was over 50% which is better than reported outcome in previously published papers describing the treatment of stage IIIA NSCLC with CRT [5,9,10]. The agreement between clinical and postoperative pathological TNM stage was observed in only 53,8%. In view of the discrepancy of clinical and pathological data, a considerable number of these patients may have been over staged.

Modern guidelines state that pneumonectomy should be avoided after CRT because of the high postoperative risk reported in earlier studies [5]. In our series, 30-day mortality after pneumonectomy/bilobectomy was only 4.3% and 5-year OS was 44%, suggesting that CRT and major surgery should remain an option in selected cases [11]. This is corroborated by a recent paper from the USA reporting 5-year OS of 35% after CRT and pneumonectomy versus 45% after CRT and lobectomy [12]. These results were, however, obtained in patients with N2-disease only, and comprised an older series (2004–2014). The pivotal North American Intergroup 0139 trial accrued patients from 1994 through 2001 and reported a 5-year OS after pneumonectomy of 22%, mainly related to high postoperative risk [5].

The 57% 5-year OS after CRT and lobectomy looks favorable compared to other treatment options, but results cannot be directly compared due to selection bias, which cannot be resolved by modern analytical methods such as propensity score matching. The opportunity for curative surgery after CRT was assessed depending on response and performance status, resulting in a highly selected population. Randomized comparisons using modern staging and treatment options are needed for proper comparison of treatment modalities, but for now, population-based data suggest that selected patients may benefit from neoadjuvant treatment.

Appropriate decision-making relies on adequate and accurate staging. Although staging in the period studied

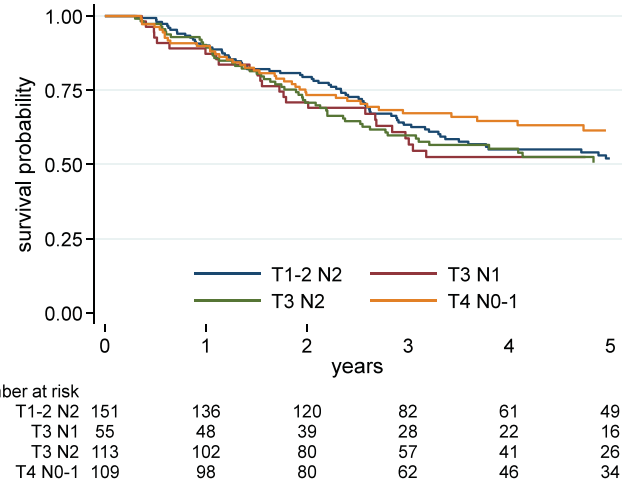

Figure 1. Prognostic impact of clinical stage category on overall survival after neoadjuvant treatment followed by a resection.

here was performed according to evidence-based treatment guidelines, an agreement between clinical and postoperative pathological TNM stage in the group of patients who underwent upfront surgery without neoadjuvant therapy was observed in 53.8% only, which has been reported before [2,13,14]. Clinical over staging was seen in 42.3% of the patients. We assume that upfront surgery was more often done in patients with 'uncertain' N2 or T3 disease, explaining the high rate of over staging. Compared to pretreatment clinical staging, downstaging was observed after neoadjuvant therapy followed by resection in 75.8% after CRT and 67.8% after chemotherapy. However, since clinical over staging in the upfront surgery group was over 40%, and the neoadjuvant therapy + resection group was staged accordingly, part of the latter group of patients without pathological confirmation of the mediastinal lymph nodes might not have had stage IIIA disease, so outcome might be overestimated. Downstaging was more common after neoadjuvant therapy with CRT as compared to chemotherapy alone, which is in accordance with previous reports [10,15]. Staging should be performed with CT-scan and FDG-PET scan, MRI or CT scan of the brain, followed by EBUS, EUS or mediastinoscopy, if considered necessary. However, in daily practice, only part of the patients indeed underwent staging by EBUS/EUS or mediastinoscopy and part of the patients was selected for surgery without mediastinal staging after discussion in a multidisciplinary tumor board meeting which is shown in previous studies [16]. Due to the introduction of minimally invasive staging tools, the accuracy of staging has improved over the past years [17].

Furthermore, a major limitation of our analyses is that it was impossible to acquire information on performance status and comorbidity in this cohort of patients. The combination of neoadjuvant treatment and surgery is reserved for the fitter and operable patients, while definitive CRT is more plausible for frail patients. Moreover, after neoadjuvant treatment, patients are generally restaged and not operated in case of the residual mediastinal disease. Without downstaging of mediastinal lymph nodes, supplementary resection will generally be declined. Because we could not control for variation in comorbidity and performance status, selection bias is not taken into account. Therefore, a direct comparison between treatment possibilities is not feasible, since several confounding factors are the present influencing outcome. Furthermore, information about the total dose of radiation was not available and different treatment methods might potentially influence survival during the follow-up period. Moreover, treatment outcome after definitive CRT has recently been strengthened by the addition of adjuvant immunotherapy in patients without the progressive disease [18,19]. In comparison with treatment with CRT alone, better PFS and OS after CRT followed by immunotherapy with durvalumab is reported and has changed the standard of care for patients with stage IIIA NSCLC [18,19]. However, in this cohort, the adjuvant immunotherapy was not standard of care yet. The combination of CRT, surgery and adjuvant immunotherapy has not been investigated yet and the role of surgery in the immunotherapy era needs to be clarified and reassessed in clinical trials.

Following Dutch guidelines and according to international standards, CRT is the most commonly applied treatment for clinical stage IIIA NSCLC. However, in the treatment of stage IIIA NSCLC, surgical resection might be of additional value in highly selected patients [13,20–24].

In comparison with previous reports, our results of population-based data show relatively high 5-year OS rates in highly selected patients who were treated with neoadjuvant therapy followed by a resection [5,22,23]. The patients selected for additional surgery were generally discussed in a multidisciplinary tumor board meeting, so selection bias was introduced. However, previous studies have shown that treatment outcomes, for example, OS, of patients with NSCLC can be improved by treatment in specialized centers with a specialized multidisciplinary thoracic oncology team [25,26]. Ongoing centralization of lung cancer surgery in The Netherlands might have partly accounted for the outcomes described here. However, as demonstrated in the current analysis, the treatment pattern still varies for stage IIIA NSCLC patients throughout The Netherlands as the proportion of neoadjuvant therapy followed by a resection varied between regions from 2.9 to 7.3%. Recently, treatment variation has also been shown for non-surgical stage IIIA NSCLC patients in The Netherlands [27]. Further centralization might lead to a more unambiguous treatment policy and may, therefore, result in an improvement of treatment outcome, as has been shown before [28,29]. The data shown here are population-based real-world data describing the treatment of clinical stage IIIA NSCLC in The Netherlands and thus present population-based results, which might be expected to be worse when compared to outcome in patients selected for clinical trials.

In conclusion, in The Netherlands, between 2010 and 2016, only 4.5% of patients with clinically staged IIIA NSCLC were selected for neoadjuvant therapy followed by resection. The 5-year OS in these patients exceeded 50%, which is relatively high compared to previously reported in phase III trials. However, clinical over staging was seen in 42.3% of the patients, so the outcome might be overestimated. It is suggested that with accurate staging, selected patients with clinically staged IIIA NSCLC may benefit from resection after neoadjuvant therapy. Patients who were treated with CRT and resection showed higher complete response rates compared to patients treated with chemotherapy followed by resection.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Integraal Kankercentrum Nederland [Internet]. Cijfers over Kanker [Figures on cancer]; 2016 [cited January 22]. Available from http://www.cijfersoverkanker.nl/selecties/Incidentie_luchtwegen/img569ff8aebef6e

[2] Dickhoff C, Dahele M, de Langen AJ, et al. Population-based patterns of surgical care for stage IIIA NSCLC in the Netherlands between 2010 and 2013. J Thorac Oncol. 2016;11(4):566–572.
[3] Postmus PE, Kerr KM, Oudkerk M, et al. Early-stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO clinical practice guidelines. Ann Oncol. 2017;28:iv1–iv21.
[4] NSCLC Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patiënts from 52 randomised clinical trials. BMJ. 1995;7(311):899–909.
[5] Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379–386.
[6] Xu XL, Dan L, Chen W, et al. 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. 2016;9(9):845–853.
[7] Damhuis RA, Maat AP, Plaisier PW. Performance indicators for lung cancer surgery in the Netherlands. Eur J Cardiothorac Surg. 2015;47(5):897–903.
[8] Ten Berge M, Beck N, Heineman DJ, et al. Dutch Lung Surgery Audit: a national audit comprising lung and thoracic surgery patients. Ann Thorac Surg. 2018;106(2):390–397.
[9] Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. Lancet. 2007;369(9577):1929–1937.
[10] Sher DJ, Fidler MJ, Liptay MJ, et al. Comparative effectiveness of neoadjuvant chemoradiotherapy versus chemotherapy alone followed by surgery for patients with stage IIIA non-small cell lung cancer. Lung Cancer. 2015;88(3):267–274.
[11] Yamaguchi M, Shimamatsu S, Edagawa M, et al. Pneumonectomy after induction chemoradiotherapy for locally advanced non-small cell lung cancer: should curative intent pulmonary resection be avoided? Surg Today. 2019;49(3):197–205.
[12] Behera M, Steuer CE, Liu Y, et al. Trimodality therapy in the treatment of stage III N2-positive non-small cell lung cancer: a national cancer database analysis. Oncologist. 2020. DOI:10.1634/theoncologist.2019-0661
[13] Dickhoff C, Hartemink KJ, Kooij J, et al. Is the routine use of trimodality therapy for selected patients with non-small cell lung cancer supported by long-term clinical outcomes? Ann Oncol. 2017;28(1):185.
[14] Boffa D, Fernandez FG, Kim S, et al. Surgically managed clinical stage IIIA-clinical N2 lung cancer in the society of thoracic surgeons database. Ann Thorac Surg. 2017;104(2):395–403.
[15] Chen Y, Peng X, Zhou Y, et al. Comparing the benefits of chemoradiotherapy and chemotherapy for resectable stage III A/N2 non-small cell lung cancer: a meta-analysis. World J Surg Onc. 2018;16(1):8.
[16] Bousema JE, van Dorp M, Hoeijmakers F, et al. Guideline adherence of mediastinal staging of non-small cell lung cancer: a multicentre retrospective analysis. Lung Cancer. 2019;134:52–58.
[17] Talebian Yazdi M, Egberts J, Schinkelshoek MS, et al. Endosonography for lung cancer staging: predictors for false-negative outcomes. Lung Cancer. 2015;90(3):451–456.
[18] Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377(20):1919–1929.
[19] Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2018;379(24):2342–2350.
[20] McElnay PJ, Choong A, Jordan E, et al. Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials. Thorax. 2015;70(8):764–768.
[21] Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. Lancet. 2015;386(9998):1049–1056.
[22] Bryan DS, Donington JS. The role of surgery in management of locally advanced non-small cell lung cancer. Curr Treat Options Oncol. 2019;20(4):27.
[23] Tong S, Qin Z, Wan M, et al. Induction chemoradiotherapy versus induction chemotherapy for potentially resectable stage IIIA (N2) non-small cell lung cancer: a systematic review and meta-analysis. J Thorac Dis. 2018;10(4):2428–2436.
[24] Pöttgen C, Eberhardt W, Stamatis G, et al. Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) – a cumulative meta-analysis of the randomized evidence. Oncotarget. 2017;8(25):41670–41678.
[25] Dransfield MT, Lock BJ, Garver RI, Jr. Improving the lung cancer resection rate in the US department of veterans affairs health system. Clin Lung Cancer. 2006;7(4):268–272.
[26] Laroche C, Wells F, Coulden R, et al. Improving surgical resection rate in lung cancer. Thorax. 1998;53(6):445–449.
[27] Walraven I, Damhuis RA, Ten Berge MG, et al. Treatment variation of sequential versus concurrent chemoradiotherapy in stage III non-small cell lung cancer patients in the Netherlands and Belgium. Clin Oncol (R Coll Radiol). 2017;29(11):e177–e185.
[28] Von Meyenfeldt EM, Gooiker GA, van Gijn W, et al. The relationship between volume or surgeon specialty and outcome in the surgical treatment of lung cancer: a systematic review and meta-analysis. J Thorac Oncol. 2012;7(7):1170–1178.
[29] Wouters MW, Gooiker GA, van Sandick JW, et al. The volume-outcome relation in the surgical treatment of esophageal cancer: a systematic review and meta-analysis. Cancer. 2012;118(7):1754–1763.