Lung Cancer 127 (2019) 76–83

Contents lists available at ScienceDirect

Lung Cancer

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

Post-treatment mortality after definitive chemoradiotherapy versus trimodality therapy for locally advanced non-small cell lung cancer

Waqar Haque[a,1], Vivek Verma[b,1], E. Brian Butler[a], Bin S. Teh[a], Chad G. Rusthoven[c,*]

[a] Department of Radiation Oncology, Houston Methodist Hospital, Houston, TX, USA
[b] Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, PA, USA
[c] Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO, USA

ARTICLE INFO

Keywords:
Non-Small cell lung cancer
Chemoradiation
Lobectomy
Pneumonectomy
Mortality

ABSTRACT

Purpose: Locally advanced non-small cell lung cancer (NSCLC) is commonly managed with either definitive chemoradiation (dCRT) or neoadjuvant chemoradiation followed by surgery (nCRT + S). This study sought to compare 30- and 90-day mortality between nCRT + S and dCRT for these patients.

Methods: The National Cancer Database was queried (2004–2014) for clinicall staged T1-3N2 or T3-4N0-1 (except T3N0) NSCLC that received nCRT + S or dCRT. Statistics included cumulative incidence analysis of 30- and 90-day mortality (before and following propensity score matching) and Cox proportional hazards regressions.

Results: Of 28,379 patients, 4063 (14.3%) underwent nCRT-S, and 24,316 (85.6%) dCRT. Of the trimodality patients, 79.2% received lobectomy, 8.2% sublobar resection, and 12.5% pneumonectomy. Trimodality therapy and age, in addition to several soceiodempographic and oncologic variables, were associated with 30- and 90-day mortality. Short-term mortality was significantly higher with nCRT + S compared to dCRT at both 30 (3.4% vs. 0.8%, $p < 0.001$) and 90days (7.5% vs. 6.6%, $p = 0.017$), which persisted following propensity matching (3.4% vs. 0.4% and 7.5% vs. 5.3% respectively, both $p < 0.001$). At both 30 and 90 days, pneumonectomy was associated with higher mortality than lobectomy (6.1% vs. 2.9% and 11.1% vs. 6.9% respectively, both $p < 0.001$).

Conclusions: Treatment with nCRT + S was associated with greater 30- and 90- day post-treatment mortality when compared to treatment with dCRT, with larger differences in observed in 30-day post-treatment mortality. These data may inform shared-decsion making among patients eligible for both aproaches.

1. Introduction

The optimal management of locally advanced, stage III non-small cell lung cancer (NSCLC) is controversial and clinician- and institution-dependent. Treatment options in this setting include: up-front surgical resection followed by chemotherapy (CT) or chemoradiotherapy (CRT), neoadjuvant CT or CRT followed by resection, neoadjuvant CT followed by resection and postoperative radiotherapy (RT), or definitive CRT followed by immunotherapy.

Of these, the two most commonly utilized paradigms in the United States (particularly for N2 disease) include definitive CRT (dCRT) and neoadjuvant CRT followed by surgery (nCRT + S) [1]. There have been two phase III trials comparing both regimens for N2 NSCLC. The Intergroup 0139 trial [2] randomized 396 patients with T1-3N2 disease to neoadjuvant concurrent CRT (45 Gy + cisplatin/etoposide) followed by resection, versus definitive concurrent CRT (61 Gy + cisplatin/etoposide). At median follow-up of nearly 70 months for survivors, the trimodality arm experienced superior progression-free survival (PFS), despite no differences in overall survival (OS). However, in a subgroup analysis of patients that underwent lobectomy (rather than pneumonectomy), trimodality therapy was associated with improved OS. Next, the German ESPATUE trial [3] enrolled 246 IIIA-IIIB patients, who underwent neoadjuvant cisplatin/paclitaxel followed by hyperfractionated CRT (45 Gy in 30 twice-daily fractions). Patient without disease progression were then randomized to resection versus a CRT boost (20–26 Gy in 10–13 daily fractions). There were no differences in PFS or OS between arms.

Proponents of bimodality management with definitive CRT often argue that the post-lobectomy OS findings in Intergroup 0139 were the result of an unplanned subset analysis, as there was no prior

* Corresponding author at: Department of Radiation Oncology, University of Colorado School of Medicine, 1665 Aurora Court, Suite 1032, Aurora, CO 80045, USA.
E-mail address: chad.rusthoven@ucdenver.edu (C.G. Rusthoven).
[1] These authors contributed equally to this article.

https://doi.org/10.1016/j.lungcan.2018.11.026
Received 20 September 2018; Received in revised form 15 November 2018; Accepted 23 November 2018

stratification for surgical technique. Moreover, receipt of lobectomy may have been a surrogate for more treatment-responsive disease (disease response being a surrogate for favorable biology and improved OS) and not necessarily all patients. An additional argument is that ESPATUE did not observe outcome differences even though only non-progressors were randomized, and progressors on nCRT in Intergroup 0139 did not receive resection. This suggests that the trimodality arm of ESPATUE was composed of patients with favorable biology, and the fact that no difference in OS was observed in all patients may mean that bimodality treatment may be the optimal treatment paradigm for most patients.

Proponents of trimodality therapy note that sleeve lobectomy approaches can potentially reduce the surgical morbidities and mortality among patients who would otherwise have required a pneumonectomy [4]. Additionally, the ESPATUE study may have been underpowered to detect outcome differences; a majority of patients therein were IIIB (6^{th} edition of TNM classification) and were more likely to develop metastatic disease than IIIA patients, thus potentially dampening the benefits of resection. Furthermore, the PFS benefit in the Intergroup 0139 trial should not be discounted, as PFS is less prone to distortion (compared to OS) by salvage therapies and from other studies correlates with prognosis [5]; although, it is notable that there were no differences in PFS in the ESPATUE trial.

Central to the debate of bimodality versus trimodality therapy were the notable findings of treatment-related mortality from Intergroup 0139. Over one-quarter of pneumonectomy patients therein experienced treatment-related mortality, which likely contributed to the lack of significant OS differences between cohorts (and prompted the unplanned subset analysis). However, ESPATUE documented five grade 5 pulmonary events, all of which occurred following lobectomy (n = 4) or bilobectomy (n = 1). Taken together, these findings have also been used to support either paradigm; dedicated trials with newer and more prudent surgical approaches could very well result in OS improvements with trimodality management, but this remains a theory without prospective evidence.

Despite the controversial nature of this topic, comparative investigations of short-term mortality following trimodality versus bimodality approaches are lacking. This is particularly important as a large proportion of patients with NSCLC may opt for a less aggressive approach if it would decrease the likelihood of immediate death [6]. Although this is clearly a barrier to shared decision-making between patients and providers, we addressed this knowledge gap by performing a dedicated analysis of a large, contemporary national database to explore 30- and 90-day mortality between nCRT + S and dCRT for locally advanced NSCLC.

2. Materials and methods

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population [7]. All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The NCDB contains information not included in the Surveillance, Epidemiology, and End Results database, including details regarding systemic therapy and RT dose. The data used in the study were derived from a de-identified NCDB file (2004–2014). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Inclusion criteria for this study were $\geq$ 18 year old patients with newly-diagnosed locally advanced NSCLC treated with dCRT or nCRT + S. Survival outcomes were calculated at 30- day and 90-day after completion of definitive treatment. For patients receiving dCRT, the 30-day and 90-day mortality were calculated from the last day of radiation therapy, and for patients treated with nCRT + S, the 30- and 90-day mortality were calculated from the day of surgery. Although the controversy in management exists to the largest degree for T1-3N2 disease, we also included T3-4N0-1 (except T3N0) cases for several reasons. The clinical stage was used for the inclusion in the present study, as this is what often guides management, and the pathologic stage was not available for patients undergoing dCRT. First, the goal of the study was to evaluate 30- and 90-day mortality between bimodality and trimodality patients; thus, it mattered little *why* patients received a particular form of therapy. Second, these cases may be "functionally" treated based on degree of main bronchial and/or carinal invasion, and/or whether staging is based on multiple tumor nodules in the same or ipsilateral lobes [8]. Third, special instances of those cases necessitate bimodality therapy (e.g., inoperability) or trimodality therapy (e.g. superior sulcus tumors [9]). Fourth, many of those cases would have been eligible for inclusion in ESPATUE [3].

Surgical therapy was defined as oncologic-quality surgery (with further subgroup analysis performed as described subsequently), including sublobar resection (SL), lobectomy, or pneumonectomy. CRT was defined as initiating CT and RT within 15 days of one another [10–12]. dCRT referred to RT doses at least 60 Gy, and for nCRT at least 45 Gy [1].

All statistical tests were two-sided, with a threshold of $p < 0.05$ for statistical significance, and were performed using STATA (version 14, College Station, TX). Prior to statistical analysis, patients were grouped by receipt of dCRT versus nCRT + S; similar to criteria from previously published studies on post-treatment mortality in early-stage NSCLC [13], patients were categorized into seven *a priori* age-based subsets (for purposes of data analysis): $\leq$ 55, 56–60, 61–65, 66–70, 71–75, 76–80, and $\geq$ 81. Baseline characteristics were first compared with chi-squared tests. Second, univariable and multivariable Cox regression was performed to evaluate predictors of 30- and 90-day mortality. The proportional hazards assumption was checked graphically, and only the variables that met the proportional hazards assumption were included in the univariable and multivariable Cox regression test. Next, raw (unadjusted) values for 30- and 90-day mortality in each age-based cohort were tabulated between both groups; the trimodality cohort was also subdivided by surgical technique for further analysis. Both 30- and 90-day outcomes were also presented as line graphs as well as cumulative incidence plots. Surgical approaches are not defined in the NCDB for a majority of patients; however, a subset analysis was performed comparing outcomes for patients getting dCRT versus nCRT + S with a video-assisted thoracoscopic surgery (VATS) approach.

Owing to imbalances between cohorts on cumulative incidence analysis, propensity score matching (PSM) was performed between the dCRT and nCRT + S arms. The matched variables included age, year, sex, race, Charlson-Deyo score, facility type, histology, T stage, and N stage (surgical technique could not be encompassed in PSM because no dCRT patient received surgery). Specifically, PSM balanced these variables through matching and provided a propensity score based on the probability of receiving treatment for the given variables [14,15]. Patients from the different groups were paired together based on the similarity of the propensity score. Patients were matched 1:1 without replacement, and standardized mean differences evaluated for large imbalances for each variable between the matched cohorts [16].

3. Results

In total, 28,379 patients met study criteria; of these, 4063 (14.3%) patients were treated with nCRT-S, and 24,316 (85.6%) with dCRT. Table 1 displays clinical characteristics of both groups. Of note, the majority of patients had N2 disease; 79.2% of the trimodality patients received lobectomy, with SL and pneumonectomy performed in 8.2%

Table 1
Demographic and clinical characteristics for all patients.

Characteristic	CRT, n = 24,316 (%)	NAC + Surgery, n = 4063 (%)	P value
Age			
≤55	3789 (15.6%)	1134 (27.9%)	< 0.001
56–60	3200 (13.2%)	668 (16.4%)	
61–65	4138 (17.0%)	764 (18.8%)	
66–70	4660 (19.2%)	705 (17.4%)	
71–75	4101 (16.9%)	480 (11.8%)	
76–80	2861 (11.8%)	238 (5.9%)	
≥81	1567 (6.4%)	74 (1.8%)	
Sex			
Male	14154 (58.2%)	2217 (54.6%)	< 0.001
Female	10162 (41.8%)	1846 (45.4%)	
Race			
White	20761 (85.4%)	3541 (87.2%)	< 0.001
African American	2966 (12.2%)	411 (10.1%)	
Other	589 (2.4%)	111 (2.7%)	
Insurance			
Medicaid	1758 (7.2%)	326 (8.0%)	< 0.001
Medicare	13710 (56.4%)	1648 (40.6%)	
Private	7100 (29.2%)	1862 (45.8%)	
Uninsured	885 (3.6%)	124 (3.1%)	
Other	863 (3.6%)	103 (2.5%)	
Charlson/ Deyo score			
0	14798 (60.9%)	2672 (65.8%)	< 0.001
1	6860 (28.2%)	1039 (25.6%)	
2	2048 (8.4%)	283 (7.0%)	
≥ 3	610 (2.5%)	69 (1.7%)	
Income			
< $46,000	16,262 (66.9%)	2345 (57.7%)	< 0.001
≥ $46,000	7224 (29.7%)	1571 (38.7%)	
Not recorded	830 (3.4%)	47 (3.6%)	
Facility			
Academic	6657 (27.4%)	1492 (36.7%)	< 0.001
Non academic	17584 (72.3%)	2544 (62.6%)	
Not recorded	75 (0.3%)	27 (0.7%)	
Histology			
Adenocarcinoma	7392 (30.4%)	1516 (37.3%)	< 0.001
Squamous cell carcinoma	11140 (45.8%)	1503 (37.0%)	
Other	5784 (23.8%)	1044 (25.7%)	
T classification			
T1	4091 (16.8%)	791 (19.5%)	< 0.001
T2	9825 (40.4%)	1713 (42.2%)	
T3	6217 (25.6%)	987 (24.3%)	
T4	4183 (17.2%)	572 (14.1%)	
N classification			
N0	4439 (18.3%)	608 (15.0%)	< 0.001
N1	3151 (13.0%)	519 (12.8%)	
N2	16726 (68.8%)	2936 (72.3%)	
Year			
2004–2006	4493 (18.5%)	791 (19.5%)	0.002
2007–2009	5311 (21.8%)	938 (23.1%)	
2010–2012	8010 (32.9%)	1359 (33.5%)	
2013–2014	6501 (26.7%)	975 (24.0%)	
Surgery type			
Sublobar resection	0 (0.0%)	333 (8.2%)	< 0.001
Lobectomy	0 (0.0%)	3224 (79.4%)	
Pneumonectomy	0 (0.0%)	506 (12.5%)	
None	24,316 (100.0%)	0 (0.0%)	

and 12.5% of cases, respectively.

Univariable and multivariable Cox regression aimed to identify predictors of 30-day and 90-day mortality (Table 2). On multivariable analysis, the following variables were independently associated with both 30- and 90-day mortality: advancing age, Caucasian race (as compared to African-Americans), non-adenocarcinoma histology, increasing N stage, and receipt of trimodality therapy (as compared to dCRT) ($p < 0.05$ for all). Additionally, the following variables were also associated with higher 90-day (but not 30-day) mortality: increasing comorbidity index and lower income ($p < 0.05$ for all). Of note, the effect size of surgical technique (using dCRT as a reference) ranged from 4.5 to 9.5 for 30-day mortality, but just 1.3–2.0 for 90-day mortality.

Unadjusted 30-day mortality figures between groups are provided in Table 3. The 30-day mortality rate for dCRT patients was 0.8%, versus 3.4% in the trimodality cohort ($p < 0.001$). When subdividing the trimodality group by surgical technique, 6.1% of pneumonectomy patients experienced 30-day mortality, which was significantly greater than the 2.9% rate for lobectomy ($p < 0.001$). Lobectomy was associated with similar mortality rates as SL (3.9%) ($p = 0.281$).

Table 4 gives unadjusted 90-day mortality rates. Although statistically higher for nCRT + S as compared to dCRT, figures were numerically more comparable (7.5% vs. 6.6%, $p = 0.017$). Pneumonectomy, lobectomy, and SL were associated with rates of 11.1%, 6.9%, and 8.1%; pneumonectomy remained statistically higher than lobectomy ($p < 0.001$), with no differences between SL and lobectomy ($p = 0.160$).

Fig. 1 illustrates unadjusted cumulative incidences of short-term mortality in the overall population (Fig. 1A) and stratified for age (Fig. 1B–H). Although patients ≤65 years of age experienced statistically similar mortality between groups, it was statistically significant for those 66 and older. However, the comparison of individuals aged ≥81 was statistically insignificant, likely given that few of those subjects underwent trimodality therapy.

PSM in the overall population confirmed the differences in mortality between the dCRT and CRT + S cohorts (Supplementary Fig. 1, $p < 0.001$). The 30-day mortality following PSM was 0.4% versus 3.4% (hazard ratio (HR) 7.750, 95% confidence interval (CI) 4.740–12.671), with values at 90 days of 5.3% versus 7.5% (HR 1.476, 95% CI 1.239–1.759). A total of 952 (23.4%) of the patients undergoing nCRT + S had a record of the surgical approach used, and of these, 207 (21.7%) were coded as having received VATS. Comparison of post-treatment mortality between patients with dCRT and those received nCRT + S using a VATS approach demonstrated no significant difference in either 30-day mortality (0.8% vs. 1.9%, HR = 2.375, 95% CI 0.883–6.389, $p = 0.072$) or 90-day mortality (6.6% vs. 5.3%, HR = 0.811, 95% CI 0.448–1.466, $p = 0.5464$) between the cohorts.

Fig. 2A and B depict the subset analysis by age group for the HR and 95% CI for 30- and 90- day post- treatment mortality. No interaction was found between age and mortality by treatment at 30-days post-treatment ($p = 0.337$), while a significant interaction was found between age and mortality by treatment at 90- days post- treatment ($p = 0.003$), suggesting larger differences in 90-day mortality after nCRT + S compared to dCRT in the setting of increasing patient age.

4. Discussion

Both bimodality and trimodality approaches are well accepted ways to manage patients with locally advanced NSCLC; however, there exists a substantial knowledge gap regarding comparative risks of short-term mortality between both paradigms. This study of a large, contemporary national database of over 28,000 patients showed that there are several independent predictors of 30- and 90-day mortality in these patients, including treatment approach, age, sociodemographics, and oncologic factors. Thirty- and 90-day mortality rates were 0.8% and 6.6% in the dCRT cohort, as compared to 3.4% and 7.5% in the nCRT + S group; the pneumonectomy subset experienced significantly higher mortality than the lobectomy group (6.1% vs. 2.9% at 30 days, 11.1% vs. 6.9% at 90 days). Mortality was higher with trimodality therapy for patients aged 66–80, but not in those ≤65. These results may better inform shared decision-making between patients and providers when weighing the options of dCRT versus nCRT + S for locally advanced NSCLC.

The surgical-related mortality figures herein are comparable to existing literature [17–22], although a major caveat that merits reiteration is the limited information in the NCDB regarding specific surgical approaches for a majority of patients (e.g. video-assisted thoracoscopic surgery versus open thoracotomy), as only 23.4% of patients

Table 2
Univariable and multivariable Cox regression for 30- and 90-day mortality.

Characteristic	30 Day mortality						90 Day mortality					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age												
Continuous	1.103	1.039-1.171	0.001	1.187	1.099-1.284	< 0.001	1.142	1.114-1.171	< 0.001	1.152	1.115-1.189	< 0.001
Year												0.005
Continuous	0.899	0.814-0.994	0.038	0.909	0.818-1.009	0.075	0.922	0.884-0.961	< 0.001	0.939	0.899-0.981	
Race												
White	1 (reference)			1 (reference)			1 (reference)			1 (reference)		
African American	0.421	0.262-0.677	< 0.001	0.516	0.319-0.834	0.007	0.596	0.504-0.706	< 0.001	0.655	0.552-0.777	< 0.001
Other	1.256	0.688-2.291	0.458	1.361	0.743-2.491	0.318	0.696	0.467-0.931	0.018	0.672	0.476-0.949	0.024
Charlson/ Deyo score												
0	1 (reference)			1 (reference)			1 (reference)			1 (reference)		
1	1.153	0.907-1.467	0.245	1.146	0.899-1.460	0.270	1.086	0.980-1.203	0.114	1.067	0.962-1.183	0.218
2	1.279	0.884-1.850	0.191	1.239	0.854-1.799	0.259	1.341	1.153-1.560	< 0.001	1.263	1.084-1.471	0.003
≥ 3	1.062	0.524-2.154	0.867	1.153	0.567-2.345	0.695	1.428	1.104-1.848	0.007	1.368	1.056-1.773	0.018
Income												
< $46,000	1 (reference)			1 (reference)			1 (reference)			1 (reference)		
≥ $46,000	1.030	0.816-1.300	0.805	0.932	0.734-1.181	0.560	0.917	0.830-1.012	0.088	0.900	0.814-0.996	0.042
Not recorded	1.328	0.787-2.242	0.288	1.194	0.706-2.019	0.508	1.099	0.870-1.389	0.428	1.045	0.827-1.322	0.711
Histology												
Adenocarcinoma	1 (reference)			1 (reference)			1 (reference)			1 (reference)		
Squamous cell carcinoma	1.983	1.500-2.621	< 0.001	1.788	1.340-2.385	< 0.001	1.630	1.456-1.825	< 0.001	1.398	1.245-1.570	< 0.001
Other	1.580	1.143-2.183	0.006	1.439	1.035-2.000	0.030	1.521	1.338-1.730	< 0.001	1.395	1.223-1.590	< 0.001
N classification												
N0	1 (reference)			1 (reference)			1 (reference)			1 (reference)		
N1	0.575	0.385-0.859	0.007	0.487	.305-0.777	0.003	0.987	0.835-1.167	0.879	1.035	0.858-1.249	0.720
N2	0.698	0.541-0.900	0.006	0.710	0.467-1.077	0.108	1.058	0.937-1.194	0.362	1.315	1.089-1.589	0.005
Management												
Chemoradiation only	1 (reference)			1 (reference)			1 (reference)			1 (reference)		
Sublobar	4.850	2.768-8.500	< 0.001	5.716	3.252-10.048	< 0.001	1.245	0.851-1.821	0.259	1.426	0.974-2.088	0.068
Lobectomy	3.528	2.756-4.516	< 0.001	4.587	3.555-5.919	< 0.001	1.061	0.922-1.220	0.410	1.291	1.119-1.488	< 0.001
Pneumonectomy	7.750	5.309-11.314	< 0.001	9.339	6.318-13.806	< 0.001	1.758	.347-2.294	< 0.001	2.006	1.53-2.626	< 0.001

Table 3
Unadjusted 30-day mortality rates by treatment type and age.

Age (years)	Outcome	Sublobar resection		Lobectomy		Pneumonectomy		All surgery		CRT	
		Number	%	Number	%	Number	%	Number	%	Number	%
All	Alive	320	96.1%	3132	97.2%	475	93.9%	3927	96.7%	24116	99.2%
	Dead	13	3.9%	92	2.9%	31	6.1%	136	3.4%	200	0.8%
≤ 55	Alive	69	97.20%	874	98.90%	171	95.50%	1114	98.20%	3763	99.3%
	Dead	2	2.80%	10	1.10%		4.50%	20	1.80%	26	0.7%
56–60	Alive	48	98.0%	513	97.3%	88	95.7%	649	97.2%	3181	99.4%
	Dead	1	2.0%	14	2.7%	4	4.4%	19	2.8%	19	0.6%
61–65	Alive	54	96.4%	603	97.6%	86	95.6%	743	97.3%	4114	99.4%
	Dead	2	3.6%	15	2.4%	4	4.4%	21	2.8%	24	0.6%
66–70	Alive	68	93.2%	532	95.7%	69	90.8%	669	94.9%	4618	99.1%
	Dead	54	6.9%	24	4.3%	7	9.2%	36	5.1%	42	0.9%
71–75	Alive	55	100.0%	367	96.3%	38	86.4%	460	95.8%	4063	99.1%
	Dead	0	0.0%	14	3.7%	6	13.6%	20	4.2%	38	0.9%
76–80	Alive	17	85.0%	186	94.4%	19	90.5%	222	93.3%	2833	99.0%
	Dead	3	15.0%	11	5.6%	2	9.5%	16	6.7%	2833	1.0%
≥ 81	Alive	9	100.0%	57	93.4%	4	100.0%	70	94.5%	1544	98.5%
	Dead	0	0.0%	4	6.6%	0	0.0%	4	5.4%	23	1.5%

undergoing nCRT + S had information regarding the surgical approach. Overall, only 21.7% of surgical patients with known information regarding surgical approach were coded as having undergone VATS surgery. It is notable that, in the present analysis, when comparing dCRT patients to those having undergone nCRT + S with VATS, no difference in post-treatment mortality was found; however, this must be interepreted with caution given that the majority of patients in the surgical cohort did not have information regarding surgical approach. Nevertheless, in contemporary time periods with increasing utilization of VATS resections [23], differences in mortality between cohorts could potentially be more modest than reflected in this analysis. However, a counterargument is that patients offered trimodality therapy in this retrospective analysis likely represented a "healthier" cohort overall, suggesting that this dataset could underestimate the difference in short-term mortality between more similar cohorts.

Based on the morphology of the cumulative incidence curves, surgery was associated with a more pronounced up-front mortality (a larger proportion of the 90-day mortality occurred within 30 days); conversely, dCRT patients seemed to experience more notable mortality between 30 and 90 days. Whereas the "early" mortality in surgical patients may reflect postoperative events, the dCRT subjects (who were almost certainly less "healthy" than the operated patients overall)

Table 4
Unadjusted 90-day mortality rates by treatment type and age.

Age (years)	Outcome	Sublobar resection		Lobectomy		Pneumonectomy		All surgery		CRT	
		Number	%	Number	%	Number	%	Number	%	Number	%
All	Alive	306	91.9%	3001	93.1%	450	88.9%	3757	92.5%	22705	93.4%
	Dead	27	8.1%	223	6.9%	56	11.1%	306	7.5%	1611	6.6%
≤ 55	Alive	68	95.8%	854	96.6%	163	91.1%	1085	95.7%	3589	94.7%
	Dead	306	4.2%	3001	3.4%	163	8.9%	49	4.3%	200	5.3%
56–60	Alive	46	93.9%	496	94.1%	85	92.4%	627	93.9%	3024	94.5%
	Dead	306	6.1%	31	5.9%	7	7.6%	41	6.1%	176	5.5%
61–5	Alive	51	91.1%	587	95.0%	82	91.1%	720	94.2%	3931	95.0%
	Dead	51	8.9%	31	5.0%	8	8.9%	44	5.8%	207	5.0%
66–70	Alive	65	89.0%	501	90.1%	62	81.6%	628	89.1%	4365	93.7%
	Dead	8	11.0%	55	9.9%	14	18.4%	77	10.9%	295	6.3%
71–75	Alive	53	96.4%	341	89.5%	35	79.60%	429	89.4%	3763	91.8%
	Dead	27	3.6%	40	10.5%	9	20.5%	51	10.6%	338	8.2%
76–80	Alive	15	75.0%	171	86.8%	19	90.5%	205	86.1%	2623	91.7%
	Dead	5	25.0%	26	13.2%	2	9.5%	33	13.9%	238	8.3%
≥ 81	Alive	8	88.9%	51	83.6%	4	100.0%	63	85.1%	1410	90.0%
	Dead	1	11.1%	10	16.4%	0	0.0%	11	14.9%	157	10.0%

might have experienced a relative increase in the number of mortality events from pre-existing cardiopulmonary and other non-cancer co-morbidities. Thus, the term “treatment-related mortality” was not used herein, because the specific causes of death are unknown. Although the effect of adjuvant CT (which is sometimes delivered following dCRT (and surgery)) cannot be excluded, this information is also not available in the NCDB. To this extent, it is worth mentioning that adjuvant immunotherapy (which is generally tolerated better than chemotherapy) is now the standard of care in this setting [24]; however, it is important to note that adjuvant immunotherapy was not standard within the time window of this analysis from 2004 to 2014.

There are several strategies to improve postoperative outcomes in patients treated with trimodality management. First, although removal of RT from the nCRT regimen could theoretically reduce postoperative mortality, a randomized trial comparing neoadjuvant chemotherapy alone to neoadjuvant CRT failed to show any difference in outcome [25]. Neoadjuvant RT dose selection may be another consideration. The Radiation Therapy Oncology Group 0229 study performed neoadjuvant dose-escalation to 60 Gy, which was associated with a 14% rate of postoperative pulmonary grade 3 events, and one (2.7%) instance of 30-day mortality [26]. Although the study is notable for displaying the efficacy of sterilizing mediastinal nodal disease by dose-escalation, it is difficult to conclude whether mediastinal downstaging would translate into an improvement in outcomes, because patients achieving nodal clearance likely have favorable tumor biology that would (in itself) predispose to a better outcome regardless of dose-escalation. Nevertheless, routine dose-escalation in the dCRT setting has shown detriments in survival [27], and thus the potential of high-dose preoperative CRT must be carefully weighed against the known risks. Next, delivery of preoperative intensity-modulated RT (IMRT) instead of three-dimensional conformal RT (3DCRT) is an attractive measure which could potentially reduce postoperative morbidity and mortality. Although there are little data in the trimodality setting for NSCLC, IMRT as part of nCRT + S for esophageal cancer displays fewer postoperative events as compared to 3DCRT-based trimodality management [28], and IMRT-based dCRT for NSCLC results in reduced treatment-related pneumonitis [29]. To this extent, neoadjuvant proton beam therapy may also be of utility and allow for safe dose-escalation while maintaining a low rate of complications, as evidenced in the definitive setting [30]. Lastly, in addition to advanced surgical techniques such as sleeve lobectomy and VATS resections, it has also been proposed that cases requiring pneumonectomy may proportionally benefit more from up-front surgery followed by adjuvant CRT [31] as opposed to neoadjuvant CRT. To this end, a randomized trial comparing neoadjuvant chemoradiation to neoadjuvant chemotherapy followed by adjuvant radiation therapy demonstrated an increase in treatment-related mortality with neoadjuvant chemoradiation amongst patients receiving a pneumonectomy [32].

This analysis has several limitations. The NCDB has several known shortcomings, such as lack of information regarding the specific cause of mortality, type/amount of chemotherapy, pre-treatment workup (including positron emission tomography and pathologic nodal staging), specifics on T staging (e.g. T3-4 based on size versus separate tumor nodules), stations and size of involved nodal disease, performance status, and pulmonary function tests [33]. Next, though the NCDB contains records on RT technique, it is often missing and/or nonspecific. Additionally, time from completion of nCRT to resection was not evaluated, but other studies demonstrate no statistical correlation with postoperative mortality [34]. Additionally, facility volume was deliberately not included as a parameter in the multivariable model for several reasons: 1) existing studies define this parameter in arbitrary and non-standardized manners (e.g. dichotomously, quartiles, etc.); 2) it would have necessitated removing a majority of the data, since the number of CoC-accredited programs varies from one year to the next, and only a minority of all facilities would be accredited for each year from 2004 to 2014; and 3) facility volume correlates highly with academic institution. In the analysis by Wang et al., the strongest predictor of treatment at a high-volume center was treatment at an academic center (odds ratio 4.28, 95% CI 3.72–4.93) [35]. Other studies have very similarly shown that academic institutions independently predict for reduced postoperative mortality [36]; thus, institution type and facility volume may be different vehicles to express the same underlying notion. Moreover, while the NCDB does have a record of the treatment that was administered, it does not describe the reason for the selected treatment. Therefore, it is possible that there was a selection bias where more healthy patients were preferentially selected for the nCRT + S treatment, or that patients initially selected for nCRT + S may have been instead treated with dCRT if the patient was found to have progressive disease. Finally, this was a retrospective review of hospital- based data and is not a replacement for a randomized clinical trial. However, there is value in observational data, as this is indicative of what occurs in the “real world” setting, and is perhaps more reflective of patient outcomes as these patients are not receiving extra care and attention within the care of a clinical trial [37].

5. Conclusions

There is a substantial knowledge gap regarding comparative risks of short-term mortality between bimodality and trimodality approaches for locally advanced NSCLC. In addition to elucidating predictors of

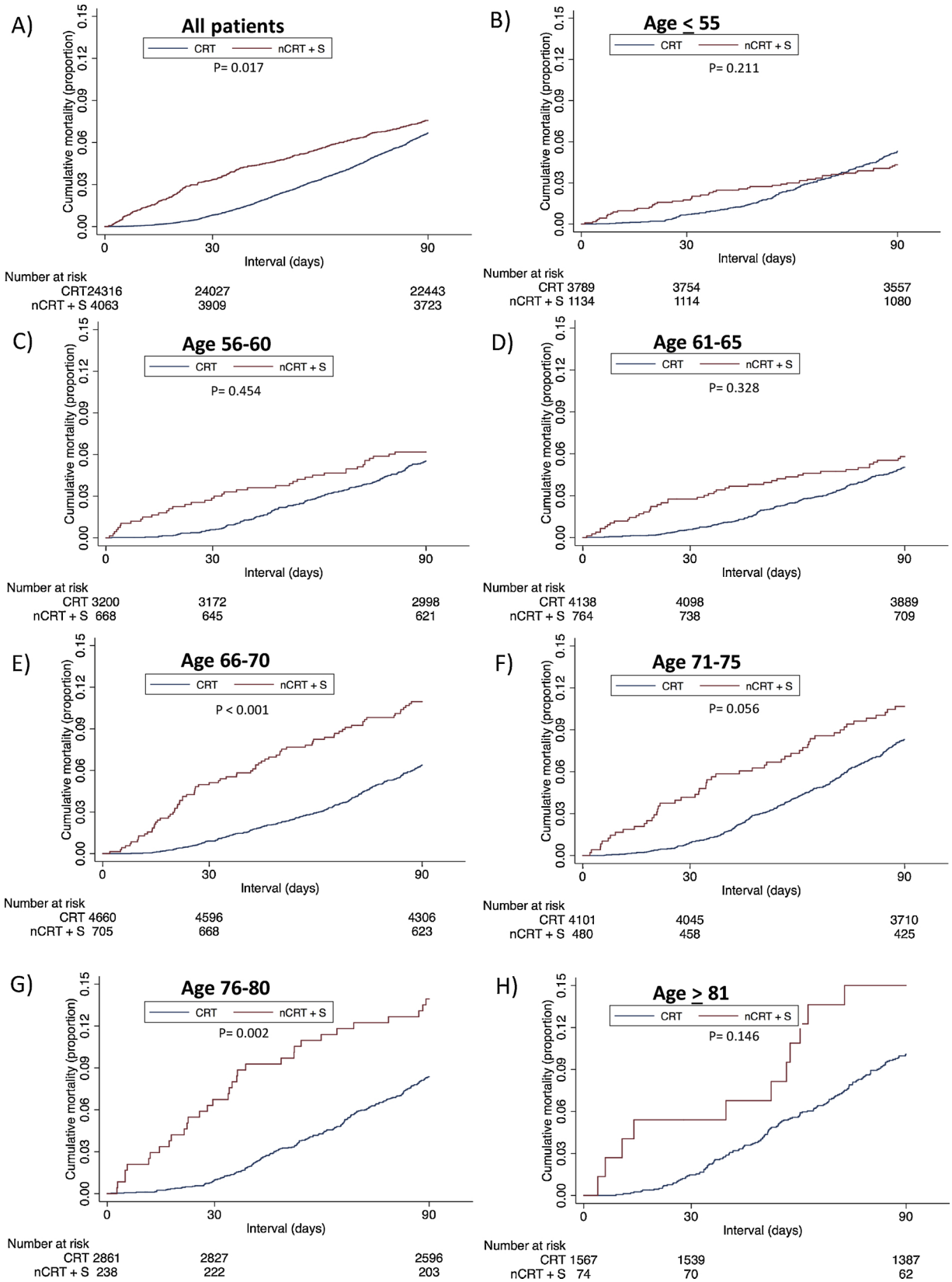

Fig. 1. Unadjusted cumulative mortality rates at 30 and 90 days for A) all patients; B) patients ≤ 55 years; C) patients 56–60 years; D) patients 61–65 years; E) patients 66–70 years; F) patients 71–75 years; G) patients 76–80 years; and H) patients ≥ 81 years.

early mortality in these patients, this investigation highlighted 30- and 90-day mortality with both paradigms (0.8% vs. 3.4% and 6.6% vs. 7.5%, respectively). The effect of age on mortality was further characterized, as well as the impact of surgical technique. These results may better inform shared decision-making between patients and providers when weighing the options of dCRT versus nCRT + S for locally

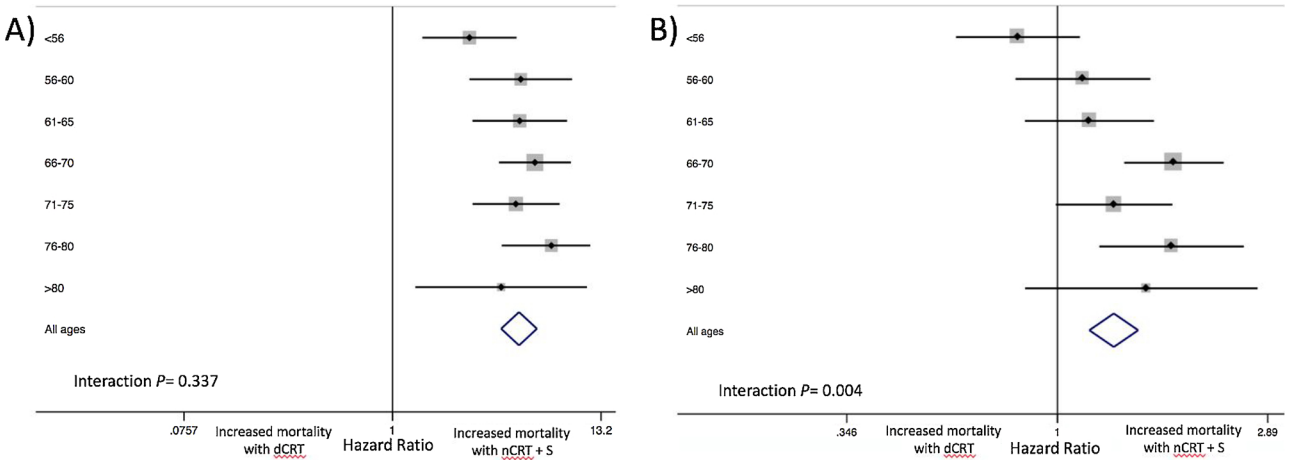

Fig. 2. Forest plot with univariate hazard ratios for mortality by age group at A) 30-days and B) 90-days post-treatment.

advanced NSCLC.

Conflict of interest

The authors assert that they have no relevant financial interests to disclose.

Disclaimers

None. This has never been presented/published before in any form. All authors declare that conflicts of interest do not exist.

Funding

There was no research support for this study.

Declaration

There are no acknowledgements. There was no funding for this study. This study has not been presented or published in part or full form elsewhere. All authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.11.026.

References

[1] National Comprehensive Cancer Network, Non-Small Cell Lung Cancer. Version 5, (2018) Accessed July 21, 2018 https://www.nccn.org/professionals/physician_gls/pdf/nsclc.pdf.
[2] K.S. Albain, R.S. Swann, V.W. Rusch, 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 374 (2009) 379–386.
[3] W.E. Eberhardt, C. Pottgen, T.C. Gauler, et al., Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE), J. Clin. Oncol. 33 (2015) 4194–4201.
[4] J. Deslauriers, J. Gregoire, L.F. Jacques, et al., Sleeve lobectomy versus pneumonectomy for lung cancer: a comparative analysis of survival and sites or recurrences, Ann. Thorac. Surg. 77 (2004) 1152–1156.
[5] A. Mauguen, J.P. Pignon, S. Burdett, et al., Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data, Lancet Oncol. 14 (2013) 619–626.
[6] B.J. McNeil, R. Weichselbaum, S.G. Pauker, Fallacy of the five-year survival in lung cancer, N. Engl. J. Med. 299 (1978) 1397–1401.
[7] K.Y. Bilimoria, A.K. Stewart, D.P. Winchester, et al., The national cancer data base: a powerful initiative to improve cancer care in the United States, Ann. Surg. Oncol. 15 (2008) 683–690.
[8] V. Patel, J.B. Shrager, which patients with stage III non-small cell lung cancer should undergo surgical resection? Oncologist 10 (2005) 335–344.
[9] V.W. Rusch, D.J. Giroux, M.J. Kraut, et al., Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160), J. Clin. Oncol. 25 (2007) 313–318.
[10] W. Haque, V. Verma, E.B. Butler, B.S. Teh, Definitive chemoradiation at high volume facilities is associated with improved survival in glioblastoma, J. Neurooncol. 135 (2017) 173–181.
[11] A.C. Moreno, W. Haque, V. Verma, P. Fang, S.H. Lin, Concurrent versus sequential chemoradiation therapy in completely resected pathologic N2 non-small cell lung cancer: propensity-matched analysis of the national cancer data base, Ann. Surg. Oncol. 25 (2018) 1245–1253.
[12] V. Verma, A.C. Moreno, W. Haque, P. Fang, S.H. Lin, Sequential versus concurrent chemoradiation therapy by surgical margin status in resected non-small cell lung cancer, J. Compr. Canc. Netw. 16 (2018) 508–516.
[13] W.A. Stokes, M.R. Bronsert, R.A. Meguid, et al., Post- treatment mortality after surgery and stereotactic body radiotherapy for early- stage non- small cell lung cancer, J. Clin. Oncol. 36 (2018) 642–651.
[14] P.C. Austin, Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to- one matching on the propensity score, Am. J. Epidemiol. 172 (2010) 1092–1097.
[15] P.R. Rosenbaum, D.B. Rubin, The central role of the propensity score in observational studies for causal effects, Biometrika 70 (1983) 15.
[16] P.C. Austin, Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples, Stat. Med. 28 (2009) 3083–3107.
[17] M. Kates, X. Perez, J. Gribetz, et al., Validation of a model to predict perioperative mortality from lung cancer resection in the elderly, Am. J. Respir. Crit. Care Med. 179 (2009) 390–395.
[18] A. Zuin, G. Marulli, C. Breda, et al., Pneumonectomy for lung cancer over the age of 75 years: is it worthwhile? Interact. Cardiovasc. Thorac. Surg. 10 (2010) 931–935.
[19] H.A. Powell, L.J. Tata, D.R. Baldwin, et al., Early mortality after surgical resection for lung cancer: an analysis of the English National Lung cancer audit, Thorax 68 (2013) 826–834.
[20] C.M. Pezzi, K. Mallin, A.S. Mendez, et al., Ninety-day mortality after resection for lung cancer is nearly double 30-day mortality, J. Thorac. Cardiovasc. Surg. 148 (2014) 2269–2278.
[21] J.E. Rosen, J.G. Hancock, A.W. Kim, et al., Predictors of mortality after surgical management of lung cancer in the National Cancer database, Ann. Thorac. Surg. 98 (2014) 1953–1960.
[22] A. Green, J. Hauge, M. Iachina, E. Jakobsen, The mortality after surgery in primary lung cancer: results from the Danish Lung Cancer registry, Eur. J. Cardiothorac. Surg. 49 (2016) 589–594.
[23] J.D. Blasberg, C.W. Seder, G. Leverson, et al., Video-assisted thoracoscopic lobectomy for lung cancer: current practice patterns and predictors of adoption, Ann. Thorac. Surg. 102 (2016) 1854–1862.
[24] S.J. Antonia, A. Villegas, D. Daniel, et al., Durvalumab after Chemoradiotherapy in stage III non–Small-Cell lung Cancer, N. Engl. J. Med. 377 (2017) 1919–1929.
[25] D.J. Sher, M.J. Fidler, M.J. Liptay, M. Koshy, Comparative effectiveness of neoadjuvant chemoradiotherapy versus chemotherapy alone followed by surgery for patients with stage IIIA non-small cell lung cancer, Lung Cancer 88 (2015) 267–274.
[26] M. Suntharalingam, R. Paulus, M.J. Edelman, et al., Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung, Int. J. Radiat. Oncol. Biol. Phys. 84 (2012) 456–463.
[27] J.D. Bradley, R. Paulus, R. Komaki, 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, Lancet Oncol. 16 (2015) 187–199.
[28] S.H. Lin, K.W. Merrell, J. Shen, et al., Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer, Radiother. Oncol. 123 (2017) 376–381.
[29] S.G. Chun, C. Hu, H. Choy, et al., Impact of intensity-modulated radiation therapy technique for locally advanced non–small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial, J. Clin. Oncol. 35 (2017) 56–62.
[30] J.Y. Chang, V. Verma, M. Li, et al., Proton beam radiotherapy and concurrent chemotherapy for unresectable stage III non-small cell lung cancer: final results of a phase 2 study, JAMA Oncol. 3 (2017) e172032.
[31] S.R. Broderick, A.P. Patel, T.D. Crabtree, et al., Pneumonectomy for clinical stage IIIA non-small cell lung cancer: the effect of neoadjuvant therapy, Ann. Thorac. Surg. 101 (2016) 451–458.
[32] M. Thomas, C. Rube, P. Hoffknecht, et al., Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomized trial in stage III non-small-cell lung cancer, Lancet Oncol. 9 (2008) 636–648.
[33] W. Haque, V. Verma, E.B. Butler, B.S. Teh, Utilization of stereotactic radiosurgery for renal cell carcinoma brain metastases, Clin. Genitourin Cancer (2018), https://doi.org/10.1016/j.clgc.2018.03.015.
[34] S.J. Gao, C.D. Corso, E.H. Wang, et al., Timing of surgery after neoadjuvant chemoradiation in locally advanced non–small cell lung cancer, J. Thorac. Oncol. 12 (2016) 314–322.
[35] E.H. Wang, C.E. Rutter, C.D. Corso, et al., Patients selected for definitive concurrent chemoradiation at high-volume facilities achieve improved survival in stage III non–small-cell lung cancer, J. Thorac. Oncol. 10 (2015) 937–943.
[36] P. Samson, A. Patel, T.D. Crabtree, et al., Multidisciplinary treatment for stage IIIA non-small cell lung cancer: does institution type matter? Ann. Thorac. Surg. 100 (2015) 1773–1779.
[37] R.E. Sherman, S.A. Anderson, G.J. Dal Pan, et al., Real-world evidence- what is it and what can it tell us? N. Engl. J. Med. 375 (2016) 2293–2297.