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Postoperative Radiotherapy for Resected Stage IIIA-N2 Non-small-cell Lung Cancer: A Population-Based Time-Trend Study

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Abstract

Introduction The value of postoperative radiotherapy (PORT) for resected stage IIIA-N2 non-small-cell lung cancer (NSCLC) is controversial with few studies focusing on whether PORT always plays a part in clinical practice and generates benefits to patients across different time periods. We investigated this issue using the Surveillance, Epidemiology, and End Results Database (SEER) and assessed the temporal trends spanning 27 years.

Methods Within SEER, we selected stage IIIA-N2 NSCLC patients who underwent a lobectomy or pneumonectomy and coded as receiving PORT or never receiving radiotherapy over three time periods: 1988 to 1996, 1997 to 2005, 2006 to 2014. For each period, survival analyses were performed and propensity score matching (PSM) was used in the potentially beneficial subgroup.

Results 45.4% of 5568 eligible patients received PORT. The yearly PORT use rates varied largely from 27.8% to 74.4%. Overall survival (OS) was distinctly improved over the period. The application of PORT had a significant impact on survival only in period 1 and 3. In subgroup analysis, the OS benefit of PORT was significant in each period in patients with 50% or more lymph node ratio (LNR) both before (hazard ratios, and P values of 0.647, $P=.002$; 0.804, $P=.008$; 0.721, $P<.001$ for period 1, 2, 3, respectively) and after PSM (0.642, $P=.006$; 0.785, $P=.004$; 0.748, $P=.003$ for period 1, 2, 3, respectively).

Conclusions The benefits of PORT are lasting and stable throughout the years in patients with LNR of 50% or more. This might provide a clue on proper patient selection for PORT application.

Keywords Non-small-cell lung cancer · Stage IIIA-N2 · Survival · Postoperative radiotherapy · Trend

Introduction

Lung cancer is the leading cause of cancer-related mortality both worldwide and in the USA [1, 2], of which non-small-cell lung cancer (NSCLC) accounts for the majority. For NSCLC without metastasis, surgical resection remains the mainstay of therapy, yet patients with positive lymph nodes have a 20–40% risk of locoregional recurrence and a more than 50% risk of distant metastasis after surgery [3, 4]. Therefore, adjuvant therapies are essential. As a systemic modality, postoperative chemotherapy is standard for patients with resected node-positive NSCLC [5, 6]. As a means to eliminate regions of microscopic disease and thus reduce locoregional recurrence and improve survival, the value of postoperative radiotherapy (PORT) remains controversial.

It is acknowledged that patients with resected stage IIIA-N2 disease are a heterogeneous population with 5-year survival rates ranging from 10 to 40% [4, 7–9]. A population-based study using the Surveillance, Epidemiology, and End Results (SEER) database from 1988 to 2002 and another one using the National Cancer Data Base (NCDB) from 2004 to 2006 showed survival benefits of PORT in N2 patients [10, 11]. Another two drew similar conclusions in pIIIA-N2 NSCLC [12, 13]. Several retrospective studies suggested

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favorable effects of PORT in pN2 disease [14–17]. However, in early randomized trials, PORT failed to improve the overall survival and results of meta-analyses were contradictory [18–21]. High-quality randomized controlled trials are still in progress to provide strong evidence. Meanwhile, large real world data are also absent regarding the value of PORT across different time periods. With all treatment methods developing and diagnosis accuracy improving, whether PORT always plays a part in clinical practice and generates survival benefits to patients are rarely explored.

The purpose of this present study was to investigate the effects of PORT on the survival of pIIIA-N2 NSCLC patients in different time periods, assess the patterns of PORT application and temporal trends spanning 27 years using a population-based dataset.

Patients and Methods

The Surveillance, Epidemiology, and End Results (SEER) database is representative of the US population, collecting population-level data from 18 cancer registries covering information on cancer incidence, patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and follow-up for vital status. Using SEER*Stat version 8.3.5 software, SEER 18 Regs Custom Data (Nov 2016 Sub) were queried to extract data from 1988 to 2014, during which the records on radiotherapy were available. This study was approved by the Institutional Review Board of Shanghai Chest Hospital.

Individuals aged 21 or more and with histologically diagnosed stage N2 NSCLC, who underwent a lobectomy or pneumonectomy and coded as receiving postoperative external beam radiation or never receiving radiotherapy, were identified. We only included patients with complete information on laterality, tumor location, grade, number of nodes examined, number of nodes positive, tumor size, extent, type of surgery, and survival data. Patients died within one month after surgery and patients with more than one primary malignancy were excluded. We restaged all the patients according to the 7th edition of American Joint Committee on Cancer TNM classification with tumor size and extent variables and ultimately included stage IIIA-N2 patients. Figure 1 details the selection process for inclusion of patients.

Consistent with the 2015 WHO classification of lung tumors [22], we categorized patients by histology into adenocarcinoma (SEER codes 8140, 8230, 8250–8255, 8260, 8310, 8323, 8480, 8481, 8490, 8550, 8570, 8572, 8574), squamous cell carcinoma (SEER codes 8052, 8070–8074, 8082–8084), and others (SEER codes 8012, 8013, 8022, 8030, 8031, 8032, 8046, 8200, 8240, 8249, 8560, 8980). Lymph node ratio (LNR) was defined as the ratio of the number of positive nodes to the number of examined nodes. Other variables included are shown in Table 1. We chose

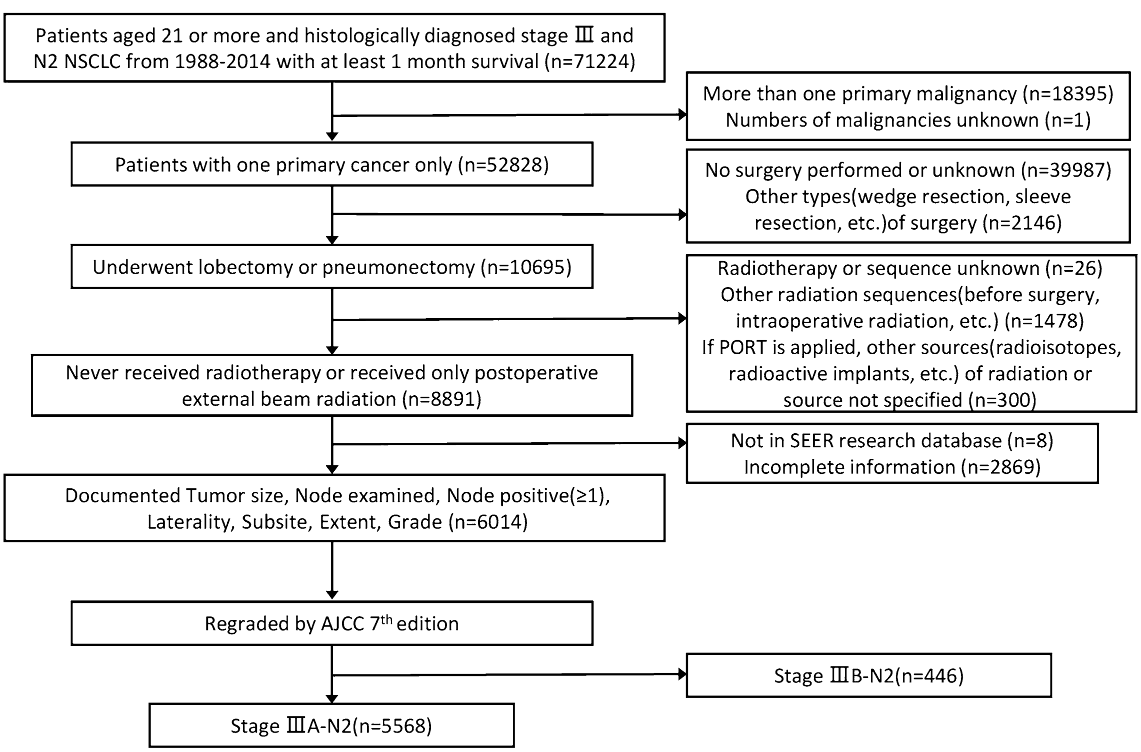

Fig. 1 Selection flow of patients

Table 1 Baseline characteristics for patients treated with or without PORT in all and each period

	1988–2014			1988–1996			1997–2005			2006–2014		
	(*N* = 5568)			(*N* = 718)			(*N* = 2020)			(*N* = 2830)		
	Non-PORT	PORT	*P*	Non-PORT	PORT	*P*	Non-PORT	PORT	*P*	Non-PORT	PORT	*P*
	N (%)	*N* (%)		*N* (%)	*N* (%)		*N* (%)	*N* (%)		*N* (%)	*N* (%)	
Sex			.496			.162			.386			.783
Male	1514 (49.8)	1284 (50.8)		137 (60.4)	269 (54.8)		538 (50.3)	496 (52.2)		839 (48.2)	519 (47.7)	
Female	1524 (50.2)	1246 (49.2)		90 (39.6)	222 (45.2)		532 (49.7)	454 (47.8)		902 (51.8)	570 (52.3)	
Age			< .001			.018			< .001			< .001
< 65	1208 (39.8)	1283 (50.7)		90 (39.6)	241 (49.1)		431 (40.3)	478 (50.3)		687 (39.5)	564 (51.8)	
≥ 65	1830 (60.2)	1247 (49.3)		137 (60.4)	250 (50.9)		639 (59.7)	472 (49.7)		1054 (60.5)	525 (48.2)	
Race			.252			.067			.908			.241
White	2492 (82.0)	2045 (80.8)		197 (86.8)	399 (81.3)		884 (82.6)	783 (82.4)		1411 (81.0)	863 (79.2)	
Non white	546 (18.0)	485 (19.2)		30(13.2)	92 (18.7)		186 (17.4)	167 (17.6)		330 (19.0)	226 (20.8)	
Laterality			.028			.843			.464			.005
Right	1593 (52.4)	1401 (55.4)		122 (53.7)	260 (53.0)		557 (52.1)	510 (53.7)		914 (52.5)	631 (57.9)	
Left	1445 (47.6)	1129 (44.6)		105 (46.3)	231 (47.0)		513 (47.9)	440 (46.3)		827 (47.5)	458 (42.1)	
Location			.007			.583			.375			.018
Main bronchus	39 (1.3)	34 (1.3)		4 (1.8)	9 (1.8)		12 (1.1)	15 (1.6)		23 (1.3)	10 (0.9)	
Upper lobe	1756 (57.8)	1530 (60.5)		136 (59.9)	305 (62.1)		637 (59.5)	591 (62.2)		983 (56.5)	634 (58.2)	
Middle lobe	122 (4.0)	132 (5.2)		6 (2.6)	21 (4.3)		52 (4.9)	48 (5.1)		64 (3.7)	63 (5.8)	
Lower lobe	1121 (36.9)	834 (33.0)		81 (35.7)	156 (31.8)		369 (34.5)	296 (31.2)		671 (38.5)	382 (35.1)	
Histology			.044			.514			.093			.018
Adeno	1916 (63.1)	1677 (66.3)		125 (55.1)	292 (59.5)		652 (60.9)	617 (64.9)		1139 (65.4)	768 (70.5)	
SCC	742 (24.4)	561 (22.2)		69 (30.4)	138 (28.1)		279 (26.1)	209 (22.0)		394 (22.6)	214 (19.7)	
Others	380 (12.5)	292 (11.5)		33 (14.5)	61 (12.4)		139 (13.0)	124 (13.1)		208 (11.9)	107 (9.8)	
Differentiation			.189			.513			.963			.218
Well differentiated	168 (5.5)	111 (4.4)		13 (5.7)	19 (3.9)		46 (4.3)	42 (4.4)		109 (6.3)	50 (4.6)	
Moderately differentiated	1263 (41.6)	1045 (41.3)		62 (27.3)	155 (31.6)		410 (38.3)	374 (39.4)		791 (45.4)	516 (47.4)	
Poorly differentiated	1492 (49.1)	1265 (50.0)		131 (57.7)	275 (56.0)		561 (52.4)	488 (51.4)		800 (46.0)	502 (46.1)	
Undifferentiated	115 (3.8)	109 (4.3)		21 (9.3)	42 (8.6)		53 (5.0)	46 (4.8)		41 (2.4)	21 (1.9)	
Tumor Stage (7th edition)			.915			.348			.638			.297
T1	798 (26.3)	652 (25.8)		56 (24.7)	114 (23.2)		295 (27.6)	254 (26.7)		447 (25.7)	284 (26.1)	
T2	1689 (55.6)	1417 (56.0)		124 (54.6)	294 (59.9)		581 (54.3)	535 (56.3)		984 (56.5)	588 (54.0)	
T3	551 (18.1)	461 (18.2)		47 (20.7)	83 (16.9)		194 (18.1)	161 (16.9)		310 (17.8)	217 (19.9)	
Nodes sampled			.002			.858			.041			.546
1–5	619 (20.4)	576 (22.8)		69 (30.4)	141 (28.7)		253 (23.6)	243 (25.6)		297 (17.1)	192 (17.6)	
6–10	937 (30.8)	839 (33.2)		69 (30.4)	158 (32.2)		332 (31.0)	329 (34.6)		536 (30.8)	352 (32.3)	

Table 1 (continued)

	1988–2014 (*N* = 5568)			1988–1996 (*N* = 718)			1997–2005 (*N* = 2020)			2006–2014 (*N* = 2830)		
	Non-PORT	PORT	*P*	Non-PORT	PORT	*P*	Non-PORT	PORT	*P*	Non-PORT	PORT	*P*
	N (%)	*N* (%)		*N* (%)	*N* (%)		*N* (%)	*N* (%)		*N* (%)	*N* (%)	
≥ 11	1482 (48.8)	1115 (44.1)		89 (39.2)	192 (39.1)		485 (45.3)	378 (39.8)		908 (52.2)	545 (50.0)	
Nodes positive			< .001			.330			.009			< .001
≤ 4	2226 (73.3)	1734 (68.5)		158 (69.6)	359 (73.1)		783 (73.2)	645 (67.9)		1285 (73.8)	730 (67.0)	
> 4	812 (26.7)	796 (31.5)		69 (30.4)	132 (26.9)		287 (26.8)	305 (32.1)		456 (26.2)	359 (33.0)	
LNR			< .001			.189			.028			< .001
< 0.5	2144 (70.6)	1584 (62.6)		126 (55.5)	298 (60.7)		695 (65.0)	572 (60.2)		1323 (76.0)	714 (65.6)	
≥ 0.5	894 (29.4)	946 (37.4)		101 (44.5)	193 (39.3)		375 (35.0)	378 (39.8)		418 (24.0)	375 (34.4)	
Type of surgery			.065			.053			.119			.001
Lobectomy	2597 (85.5)	2206 (87.2)		163 (71.8)	385 (78.4)		885 (82.7)	810 (85.3)		1549 (89.0)	1011 (92.8)	
Pneumonectomy	441 (14.5)	324 (12.8)		64 (28.2)	106 (21.6)		185 (17.3)	140 (14.7)		192 (11.0)	78 (7.2)	

PORT postoperative radiotherapy, *Adeno* adenocarcinoma, *SCC* squamous cell carcinoma, *LNR* lymph node ratio

these grouping criteria which might be stratification factors that affect the prognosis after referring to previous studies and pretests.

To assess the temporal trends, all cases were divided into 3 diagnosis periods of 9 years each (1988–1996, 1997–2005, 2006–2014). Pearson's chi-square test or Fisher's exact test was used to compare categorical variables between the PORT and non-PORT groups, as appropriate. Multivariable binary Logistic regression was used to explore independent factors for PORT use, with factors significant at the 0.20 α level from univariable modeling. Survival rates for all cases, each period and subgroups were assessed with Kaplan–Meier method, log-rank test and multivariable hazard ratios were estimated from Cox proportional hazards models, respectively. Then we conducted 1:1 propensity score matching (PSM) using nearest-neighbor matching with 0.03 matching tolerance to balance the baseline in the potentially beneficial subgroup and again performed the survival analyses. Overall survival (OS) was defined as the time from diagnosis to any death. Lung cancer-specific survival (LCSS) was defined as the time from diagnosis to lung cancer-related death. X-Tile software (version 3.6.1, Yale University, New Haven, CT) was used to pretest for LNR cut point optimization. The statistical analyses were computed using SPSS (version 22.0, SPSS Inc., Chicago, IL) and GraphPad Prism 8.0.2 (GraphPad Software, San Diego, CA). Two-sided $P < 0.05$ was considered statistically significant.

Results

A total of 5568 patients were identified, including 718, 2020, 2830 patients in period 1(1988–1996), 2(1997–2005), 3(2006–2014) respectively. The median time to death or the last follow-up of all patients was 23 months (range 1–298) and of those alive it was 42 months (range 1–279). Patient demographic and clinical characteristics are compared in Table 1.

In the whole cohort, 2530 patients (45.4%) received PORT. 491 (68.4%), 950 (47.0%), and 1089 (38.5%) patients received PORT in period 1, 2, and 3 respectively. The optimal cut-off points of LNR, which could best divide the cohort into long and short survival by X-tile, were 0.56, 0.60, 0.56, and 0.59 for the whole cohort, for period 1, 2, and 3, respectively. Yet 0.5 could be statistically significant as a prognostic cut-off value as well. Considering the consequence of previous studies and clinical simplicity, we set 0.5 as the cut-off ratio in subsequent analyses. Predictors ($P < 0.05$) for PORT use were age, tumor laterality, tumor site, the number of examined lymph nodes, the number of positive lymph nodes, LNR, and surgery type by multivariable binary Logistic regression. The 5-year OS rates were significantly improved over the three periods ($P < 0.001$) in

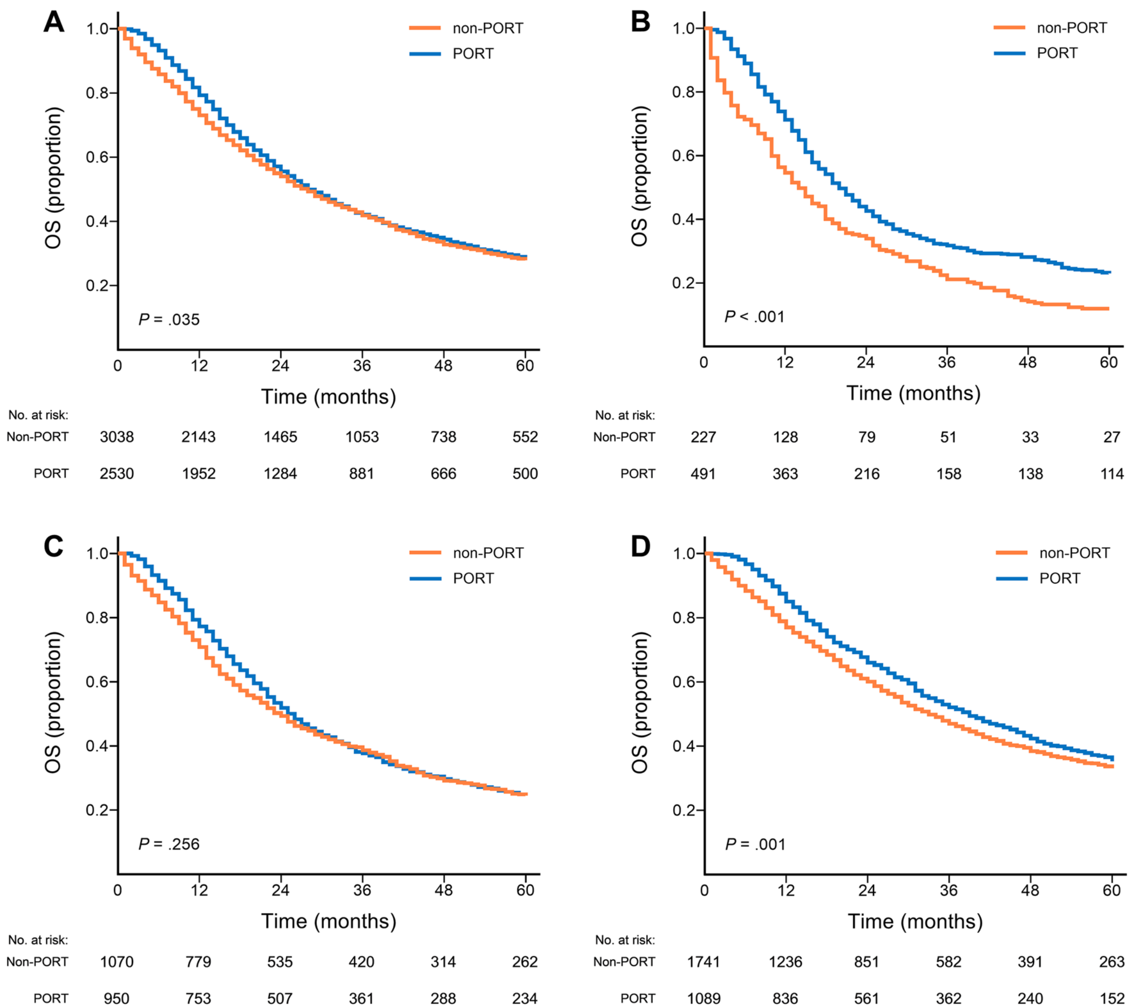

Fig. 2 Kaplan–Meier curves of overall survival (OS) for patients in all years (**a**) and period 1 (**b**), 2 (**c**), 3 (**d**) stratified by PORT use

the whole cohort (20%, 25%, 35%), non-PORT group (12%, 25%, 36%), and PORT group (23%, 25%, 36%), respectively (Supplementary Fig. 1). So were the 5-year LCSS rates (Supplementary Fig. 2). Median OS in the three periods were 20 versus 14, 26 versus 24, and 39 versus 33 months for PORT versus non-PORT group. Median LCSS in the three periods were 22 versus 18, 28 versus 28, 45 versus 39 months for PORT vs non-PORT group.

On univariable survival analysis, PORT was associated with superior OS in the whole population ($P=0.035$) and in period 1 ($P<0.001$) and 3 ($P=0.001$), but not in period 2 ($P=0.256$) (Fig. 2a–d). PORT was associated with superior LCSS in period 1 ($P=0.001$) and 3 ($P=0.015$), but not in period 2 ($P=0.316$) or in the whole population ($P=0.197$). On multivariable analysis, the Cox proportional hazards models were constructed with sex, age, race, histology, differentiation, tumor stage, LNR, type of surgery, and the use of PORT. PORT reduced 27.4% hazard of death in period 1 (HR = 0.726, 95%CI 0.609–0.856, $P<0.001$) and reduced 17.9% hazard of death in period 3 (HR = 0.821, 95%CI 0.736–0.916, $P<0.001$).

In subgroup analyses, 1840 patients (294, 753, and 793 in period 1, 2, and 3 respectively) with LNR of 50% or more were eligible. 193 (65.6%), 378 (50.2%), and 375 (47.3%) of them received PORT in period 1, 2, and 3 respectively. The OS benefits of PORT were statistically significant in each period in this subgroup both in univariable analyses (Period 1: $P=0.005$; Period 2: $P=0.020$; Period 3: $P<0.001$) and multivariable analyses (Period 1: HR = 0.647, 95% CI: 0.492–0.853, $p=0.002$; Period 2: HR = 0.804, 95% CI: 0.685–0.943, $P=0.008$; Period 3: HR = 0.721, 95% CI:0. 600–0.866, $P<0.001$). Similarly, the LCSS benefits of PORT were also significant in each period in this subgroup both in univariable analyses (Period 1: $P=0.045$; Period 2: $P=0.010$; Period 3: $P=0.001$) and multivariable analyses (Period 1: HR = 0.709, 95% CI: 0.527–0.953, $P=0.023$; Period 2: HR = 0.775, 95% CI: 0.654–0.919, $P=0.003$; Period 3: HR = 0.744, 95% CI: 0.613–0.902, $P=0.003$).

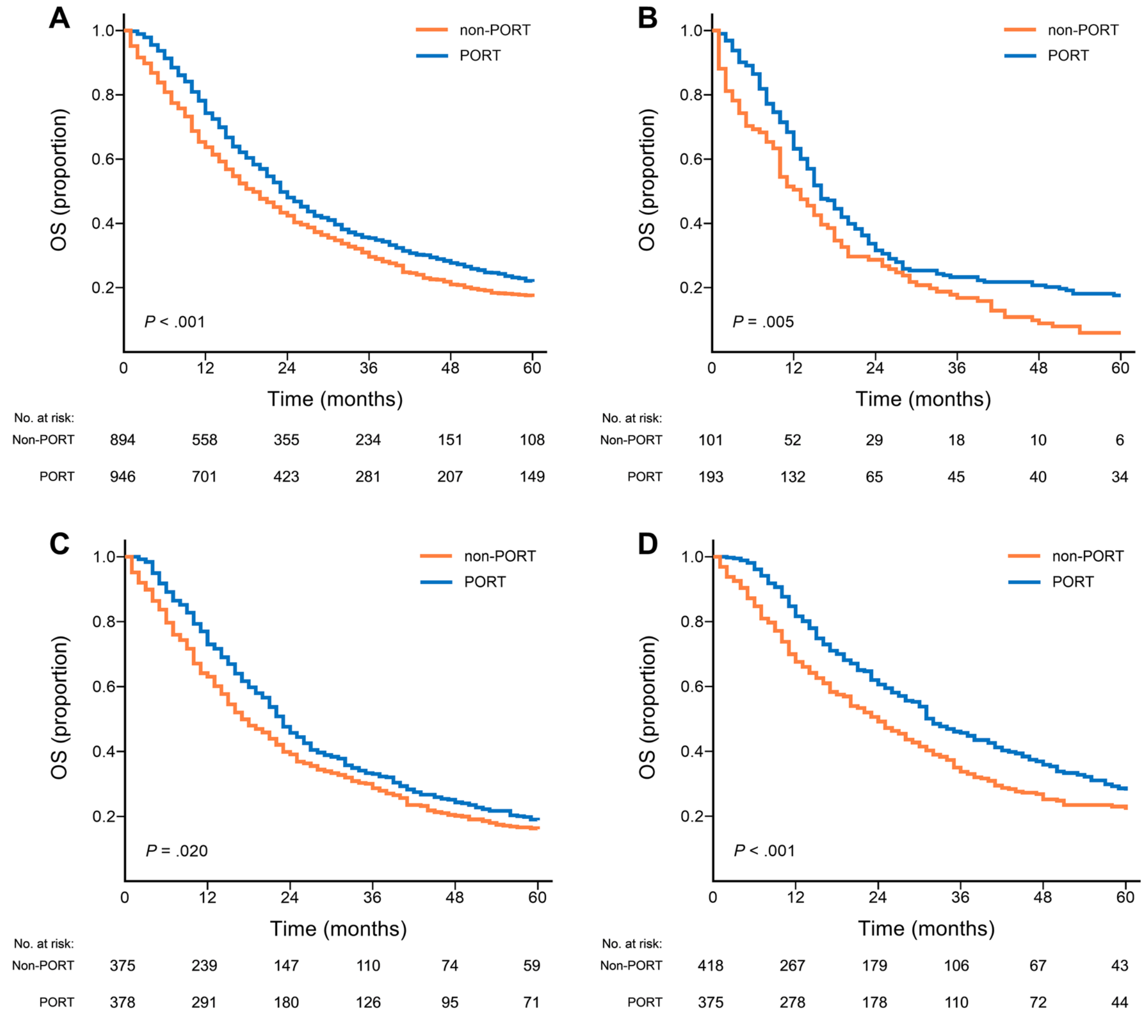

Fig. 3 Kaplan–Meier curves of overall survival (OS) for patients with LNR ≥ 50% in all years (**a**) and period 1 (**b**), 2 (**c**), 3 (**d**) stratified by PORT use

Figure 3 presents the OS curves for patients in this subgroup. On the other hand, there were 424, 1267, and 2037 patients of LNR less than 50% with 70.3%, 45.1%, and 35.1% PORT use rates in period 1, 2, and 3, respectively, and PORT was not helpful in each time period in these patients.

After PSM adjusting sex, age, race, laterality, location, histology, differentiation, T stage, number of resected nodes, number of positive nodes, and surgery type in LNR 50% or more subgroup, the baseline characteristics were well balanced between the PORT and non-PORT group in each time period (Supplementary Tables 1, 2). PORT still had a significant favorable influence on OS and LCSS in every time period. These results are summarized in Table 2.

Figure 4 demonstrates the patterns of PORT use. Among all patients, the yearly PORT use percentage ranged from the highest 74.4% in 1994 to the lowest 27.8% in 2005, as the line remained stable from the beginning but descended during the mid-1990′s and ascended slowly from the year 2005 (Fig. 4a). Among patients with LNR of 50% or more (Fig. 4b), the percentage also fluctuated and reached the lowest in 2005. In addition, when the trend of PORT use was observed by LNR, the pattern of period 1 was distinguishing (Fig. 5).

Discussion

The use of PORT in resected stage IIIA-N2 NSCLC patients has been researched for long and remains on debate [23, 24]. Compared with previous population-based studies [10–13], we covered the longest time during which the radiation codes in SEER database were obtainable and restaged patients to AJCC 7th edition using SEER extent code. The newest 8th staging edition could not be applied, however, for there were some detailed information necessary for edition transformation that could not be identified in SEER codes.

Table 2 Summarized survival analyses for patients with LNR ≥ 50% before and after propensity score matching

Time	Group	Before PSM								After PSM							
		Univariate analysis				Multivariate analysis				Univariate analysis				Multivariate analysis			
		OS		LCSS		OS		LCSS		OS		LCSS		OS		LCSS	
		5-Year Rate (%)	*P*	5-Year Rate (%)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	5-Year Rate (%)	*P*	5-Year Rate (%)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
1988–1996	PORT	18	.005	22	.045	0.647 (0.492–0.853)	.002	0.709 (0.527–0.953)	.023	17	.014	23	.043	0.642 (0.467–0.883)	.006	0.673 (0.478–0.949)	.024
	n-P	6		9		1.00 (Ref)		1.00 (Ref)		6		9		1.00(Ref)		1.00(Ref)	
1997–2005	PORT	19	.020	24	.010	0.804 (0.685–0.943)	.008	0.775 (0.654–0.919)	.003	19	.014	24	.005	0.785 (0.666–0.926)	.004	0.757 (0.635–0.902)	.002
	n-P	16		20		1.00 (Ref)		1.00(Ref)		15		18		1.00(Ref)		1.00(Ref)	
2006–2014	PORT	28	< .001	32	.001	0.721 (0.600–0.866)	< .001	0.744 (0.613–0.902)	.003	27	.011	31	.021	0.748 (0.616–0.908)	.003	0.763 (0.622–0.936)	.010
	n-P	23		28		1.00 (Ref)		1.00(Ref)		25		29		1.00(Ref)		1.00(Ref)	

PSM propensity score matching, *OS* overall survival, *LCSS* lung cancer-specific survival, *HR* hazard ratio, *CI* confidence interval, *n-P* non-PORT, *Ref* reference

We performed survival analyses and investigated the trends and subgroups in different time periods with one consistent inclusion criterion, which could make it more reasonable to illustrate the outcome.

As shown in Fig. 4, the yearly PORT use varied largely. SEER program added registries in 1992 and 2000, hence the absolute number of patients was more than before and was more representative [25]. The first half of our line chart, from 1988 to 2002, was similar to the ones reported before by Lally et al. and Bekelman et al. [10, 26]. They included all N2 patients but we only included stage IIIA-N2 patients, so the percentage for each year did not match exactly but the same trend emerged. We showed the percentage data after 2002 for the first time. This dramatic shift in the pattern of practice might be related to the publications of PORT meta-analysis in the 1990′s which found no survival benefits in PORT group and the retrospective studies in the first several years of twenty-first century which supported PORT in N2 patients. The development of radiation technology, bringing in better conformity and less side effects, perhaps additionally contributed to the increasing application of PORT in modern times [27].

The observed survival improvements over the years are likely attributed to plenty of factors such as advances in minimally invasive surgery with less complications, radiotherapy technology from conventional 2-dimensinal era to 3-dimensinal conformity and intensity modulated radiation therapy, chemotherapy regimens, novel targeted treatments, or immunotherapy [27–31]. The application of PET/CT scan in the twenty-first century made the cancer staging more precise and attributed to improved survival [32]. The 5-year survival rates in our data are consistent with previous studies.

On univariate and multivariate analyses, PORT improved OS and LCSS in period 1 and 3, but not in period 2 (1997–2005). Notably, it is hard to say why the efficacy of PORT has decreased during period 2 when the use of PORT was decreased. One plausible explanation could be the inclusion bias, as there was no record on surgical margin status in SEER. After the publication of the PORT meta-analysis, maybe fewer negative margin patients were suggested by their health providers to receive PORT, thus the number of patients who received PORT decreased and the proportion of positive margin patients in PORT group might increase in period 2. That might skew the results toward negative.

The heterogeneity of stage IIIA-N2 NSCLC patients made the treatment complex and varied. Personalized treatment is critical. Nevertheless, there was no consensus on the accurate definition for the subgroup with high locoregional recurrence risk, which might benefit more from PORT. Feng et al. proposed a three-factor model with smoking history, clinical N stage, and number of positive lymph nodes as

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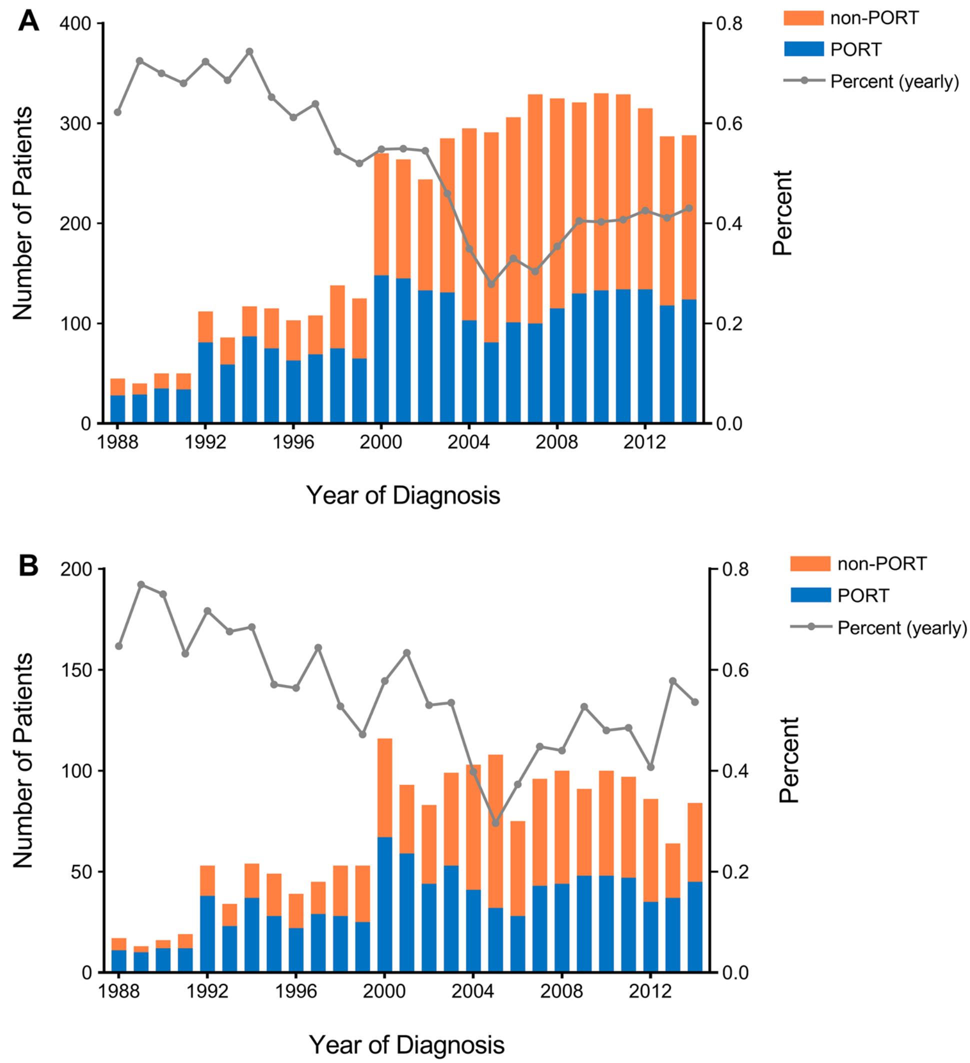

Fig. 4 Patterns of PORT use in all patients (**a**) and in patients with LNR ≥ 50% (**b**). The orange bars represent the number of patients without receiving PORT. The blue bars represent the number of patients receiving PORT. The gray line shows the percentage of yearly PORT use

prognostic index (PI) and found that PORT had different effects on patient with high or low PI [33]. Here we defined LNR as a marker of high risk after referring to analyses by X-tile and studies on breast, colon, and esophageal cancer [34–36]. The intrinsic biological causes might be that patients with higher ratio encounter higher risk of locoregional recurrence and that tumor infiltrating lymphocytes might reflect the interaction of immune system and radiation. Previously Urban et al. reported that the survival benefits of PORT limited to NSCLC patients with LNR of 50% or more using SEER database between 1998 and 2009 [37]. Our data reinforced that viewpoint and expanded the time period to make it more convincing. We also demonstrated that in real world events, the percentage of patients receiving PORT with LNR of 50% or more fluctuated a lot (Fig. 4b). The distinguishing pattern of PORT use in period 1 was possibly related to the limited cognition of the disease then, and in recent years it showed the positive relation between PORT use rate and LNR (Fig. 5). Collectively, taking the development of treatment modalities with time changing and possible bias into consideration, PORT still had favorable effects in every period both before and after PSM in patients with LNR of 50% or more. This subgroup could conceivably be the potentially beneficial group and might be treated with particular concern.

As a retrospective study, potential errors or biases are inevitable. Even after PSM, there were still unadjusted confounding factors. Demographic information regarding smoking history, performance status, and clinical pathologic information regarding the clinical stage before surgery, subclass (N2a1, N2a2, and N2b) of positive lymph nodes, surgical margin status, gene mutation status, and comorbidity were unavailable in our data. Usually patients with positive margin, less comorbidity, and better performance status score are more likely to receive PORT and all these factors could have an impact on survival. Moreover, the detailed parameters of radiation therapy such as dose, which is of importance [38], and fractionation, radiation technology,

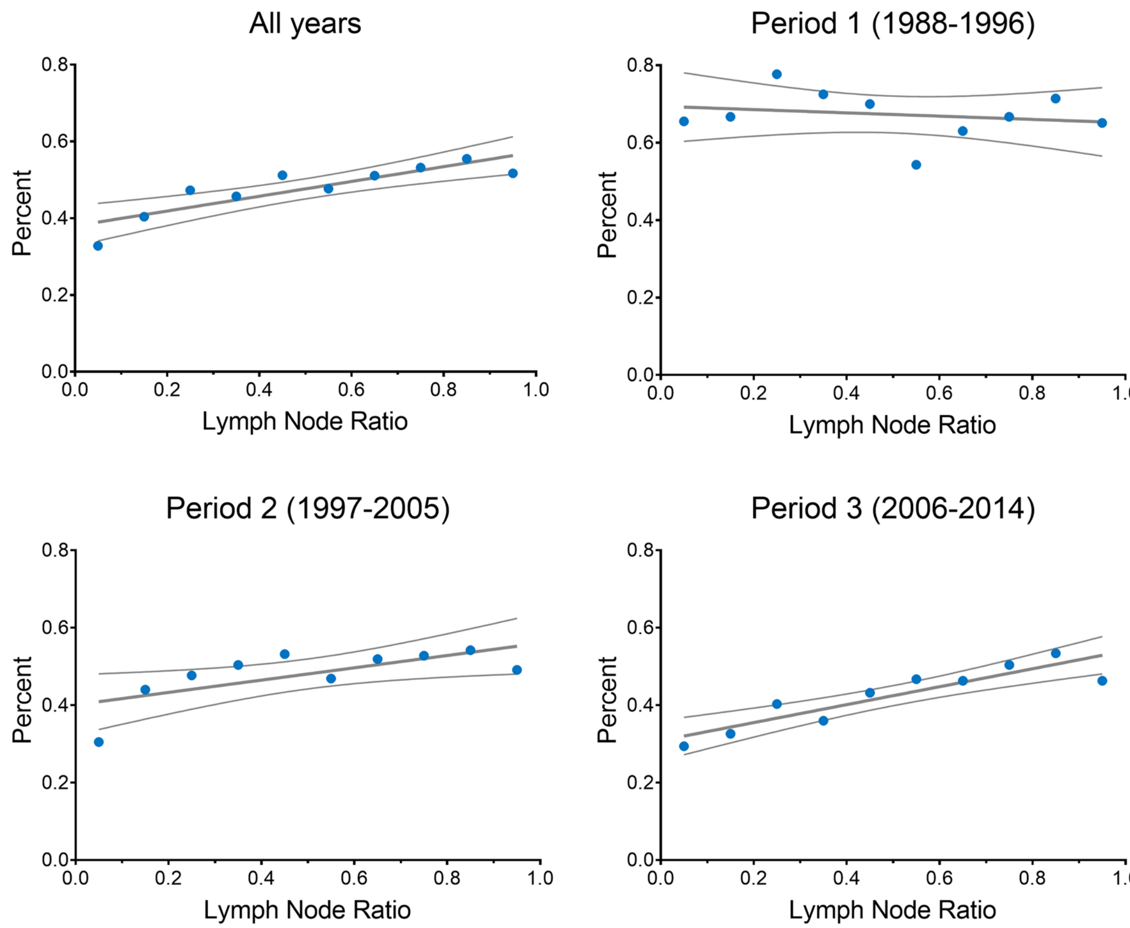

Fig. 5 Trends of PORT use by LNR for all years, and period 1, 2, and 3. The blue dots represent the PORT use rates for patients with a ten-equal-interval range of LNR (i.e., for patients with LNR > 0 and ≤ 10%, LNR > 10% and ≤ 20%, LNR > 20% and ≤ 30%, etc.). The gray lines are linear regressions and 95% CIs of the dots

and treatment sequence (concurrent or sequential) were absent. The variables of chemotherapy, targeted treatments, and immunotherapy were not available, either. It was indeed a shortcoming that information on chemotherapy was not available in SEER. Yet from the LACE meta-analysis and other studies we could find that throughout the years [29, 39], adjuvant chemotherapy could only bring limited survival benefits to the locally advanced NSCLC patients. We carried out the analysis among large population across different time periods and during these periods the patterns of chemotherapy use might be different too, but PORT still had favorable effect in the selected subgroup. Overall, despite there existed limitations, the large sample size might reduce the bias to some extent. Besides, we excluded patients with neoadjuvant therapy, who were also worth investigating though, as this current study focused on postoperative radiotherapy. We are looking forward to the outcomes of randomized clinical trials concerning the use of PORT in locally advanced NSCLC such as NCT00410683 (Lung ART), and our results need further validation in retrospective and prospective studies.

Conclusions

This population-based study demonstrates the patterns of PORT use and distinct improvements in OS of these selected resected stage IIIA-N2 NSCLC patients from 1988 to 2014. The benefits of PORT are not significant in each time period but are lasting and stable throughout the years in patients with LNR of 50% or more, although other integrated factors such as the progress of surgery and medication may contribute to a better survival. This might provide a clue on proper patient selection for PORT use. Further investigations are warranted.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed Consent Informed consent was not required as this is a retrospective study using an open population-based dataset.

Research Involving Human Participants or Animals This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424
2. Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA Cancer J Clin 69:7–34
3. Le Pechoux C (2011) Role of postoperative radiotherapy in resected non-small cell lung cancer: a reassessment based on new data. Oncologist 16:672–681
4. Detterbeck FC, Boffa DJ, Tanoue LT (2009) The new lung cancer staging system. Chest 136:260–271
5. National Comprehensive Cancer Network. NCCN Guidelines in Non-small-cell lung cancer (Version 3. 2019). https://www.nccn.org. Accessed 21 March 2019
6. Eberhardt WE, De Ruysscher D, Weder W et al (2015) 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol 26:1573–1588
7. Andre F, Grunenwald D, Pignon JP et al (2000) Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol 18:2981–2989
8. Lorent N, De Leyn P, Lievens Y et al (2004) Long-term survival of surgically staged IIIA-N2 non-small-cell lung cancer treated with surgical combined modality approach: analysis of a 7-year prospective experience. Ann Oncol 15:1645–1653
9. Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018
10. Lally BE, Zelterman D, Colasanto JM et al (2006) Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 24:2998–3006
11. Mikell JL, Gillespie TW, Hall WA et al (2015) Postoperative radiotherapy is associated with better survival in non-small cell lung cancer with involved N2 lymph nodes: results of an analysis of the National Cancer Data Base. J Thorac Oncol 10:462–471
12. Robinson CG, Patel AP, Bradley JD et al (2015) Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the National Cancer Data Base. J Clin Oncol 33:870–876
13. Herskovic A, Mauer E, Christos P et al (2017) Role of postoperative radiotherapy in pathologic stage IIIA (N2) non-small cell lung cancer in a prospective nationwide oncology outcomes database. J Thorac Oncol 12:302–313
14. Douillard JY, Rosell R, De Lena M et al (2008) Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the Adjuvant Navelbine International Trialist Association (ANITA) randomized trial. Int J Radiat Oncol Biol Phys 72:695–701
15. Dai H, Hui Z, Ji W et al (2011) Postoperative radiotherapy for resected pathological stage IIIA-N2 non-small cell lung cancer: a retrospective study of 221 cases from a single institution. Oncologist 16:641–650
16. Mantovani C, Levra NG, Filippi AR et al (2013) Postoperative radiotherapy for patients with completely resected pathologic N2 non-small-cell lung cancer: a retrospective analysis. Clin Lung Cancer 14:194–199
17. Feng W, Zhang Q, Fu XL et al (2015) The emerging outcome of postoperative radiotherapy for stage IIIA (N2) non-small cell lung cancer patients: based on the three-dimensional conformal radiotherapy technique and institutional standard clinical target volume. BMC Cancer 15:348
18. PORT Meta-analysis Trialists Group (1998) Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. The Lancet 352:257–263
19. PORT Meta-analysis Trialists Group (2005) Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2: CD002142
20. Billiet C, Decaluwe H, Peeters S et al (2014) Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. Radiother Oncol 110:3–8
21. Burdett S, Rydzewska L, Tierney J et al (2016) Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 10:CD002142
22. Travis WD, Brambilla E, Nicholson AG et al (2015) The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 10:1243–1260
23. Wagner H (2000) Postoperative adjuvant therapy for patients with resected non-small cell lung cancer: still controversial after all these years. Chest 117:110S–118S
24. Billiet C, Peeters S, Decaluwe H et al (2016) Postoperative radiotherapy for lung cancer: is it worth the controversy? Cancer Treat Rev 51:10–18
25. National Cancer Institute, Surveillance, Epidemiology, and End Results Program. Registry Groupings in SEER Data and Statistics. https://seer.cancer.gov/registries/terms.html Accessed 21 March 2019
26. Bekelman JE, Rosenzweig KE, Bach PB et al (2006) Trends in the use of postoperative radiotherapy for resected non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 66:492–499
27. Baumann M, Krause M, Overgaard J et al (2016) Radiation oncology in the era of precision medicine. Nat Rev Cancer 16:234–249
28. Klapper J, D'Amico TA (2015) VATS versus open surgery for lung cancer resection: moving toward a minimally invasive approach. J Natl Compr Canc Netw 13:162–164
29. NSCLC Meta-analyses Collaborative Group (2010) Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 375:1267–1277
30. Wang J, Zhou Z, Liang J et al (2016) Intensity-modulated radiation therapy may improve local-regional tumor control for locally advanced non-small cell lung cancer compared with three-dimensional conformal radiation therapy. Oncologist 21:1530–1537

31. Hirsch FR, Scagliotti GV, Mulshine JL et al (2017) Lung cancer: current therapies and new targeted treatments. Lancet 389:299–311
32. Grootjans W, de Geus-Oei LF, Troost EG et al (2015) PET in the management of locally advanced and metastatic NSCLC. Nat Rev Clin Oncol 12:395–407
33. Feng W, Fu XL, Cai XW et al (2016) The differential impact of postoperative radiation therapy for completely resected stage IIIA (N2) non-small cell lung cancer: Based on the risk prediction model for locoregional recurrence. Int J Radiat Oncol Biol Phys 96:S69
34. Vinh-Hung V, Verkooijen HM, Fioretta G et al (2009) Lymph node ratio as an alternative to pN staging in node-positive breast cancer. J Clin Oncol 27:1062–1068
35. Berger AC, Sigurdson ER, LeVoyer T et al (2005) Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol 23:8706–8712
36. Kelty CJ, Kennedy CW, Falk GL (2010) Ratio of metastatic lymph nodes to total number of nodes resected is prognostic for survival in esophageal carcinoma. J Thorac Oncol 5:1467–1471
37. Urban D, Bar J, Solomon B et al (2013) Lymph node ratio may predict the benefit of postoperative radiotherapy in non-small-cell lung cancer. J Thorac Oncol 8:940–946
38. Corso CD, Rutter CE, Wilson LD et al (2015) Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the National Cancer Database. J Thorac Oncol 10:148–155
39. Pignon JP, Tribodet H, Scagliotti GV et al (2008) Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 26:3552–3559