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Adjuvant Treatment Following Irradical Resection of Stage I-III Non-small Cell Lung Cancer: A Population-based Study

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ABSTRACT

Irradical (R1-2) resection for non-small cell lung cancer (NSCLC) is associated with a dismal prognosis. Adjuvant treatment attempts to improve survival outcomes, but evidence on the optimal strategy is limited. The purpose of this study was to compare overall survival (OS) between different adjuvant treatment strategies in these patients.

Out of 8,528 patients with newly diagnosed NSCLC from 2015-2018, those with an R1-2 resection were identified from the Netherlands Cancer Registry. First, OS was compared between adjuvant treatment groups 'no therapy', 'radiotherapy (RT) only', 'chemotherapy only', and 'chemo- and radiotherapy (CRT)' using multinomial propensity score-weighted Cox regression analysis. Second, three 1:1 propensity score-matched sets were created for chemotherapy vs no chemotherapy, RT only vs no therapy, and CRT vs chemotherapy only. Kaplan-Meier and Cox regression analyses for OS were performed in each set.

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With a median follow-up of 23 months, 427 patients were selected. In the weighted regression analysis, compared to no adjuvant therapy, chemotherapy and CRT were associated with improved OS (HR 0.41, 95%CI: 0.22-0.76; and HR 0.55, 95%CI: 0.37-0.81, respectively), whereas RT was not (HR 1.04, 95%CI: 0.73-1.50). In the matched sets, OS was improved after chemotherapy (+/- RT) compared to no chemotherapy (HR 0.47, 95%CI: 0.32-0.69). No OS difference was observed between matched groups of RT only vs no adjuvant therapy (HR 1.13, 95%CI: 0.74-1.72), nor for CRT vs chemotherapy only (HR 1.37, 95%CI: 0.70-2.71). Adjuvant chemotherapy, but not radiotherapy, improves survival after an R1-2 resection in stage I-III NSCLC.

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide, with over 1.7 million lung cancer deaths in 2018.[1] Stage I-II and some stage III patients in whom the tumor is considered resectable, often are treated by surgery with the aim of a radical (R0) resection. An irradical (R1-2) resection occurs in 2-17%[2-4] and is associated with decreased overall survival (OS) compared to an R0 resection.[3]

The residual cancer left in situ after an irradical resection provides a rationale for adjuvant treatment. However, current evidence on the optimal adjuvant approach is limited.[5, 6] Large studies are scarce and retrospective in nature due to the relative rarity of an R1-2 resection. One prospective randomized study from 1994 compared adjuvant RT vs chemoradiotherapy (CRT) in 164 patients.[7] Recurrence-free survival was significantly longer after CRT and in the first year disease-specific survival and OS were significantly increased after CRT.[7] The largest studies assessing adjuvant RT or chemotherapy after incomplete resection include two retrospective studies that analyzed the effect of adjuvant therapy after irradical resections in respectively 5,335 and 3,461 patients with NSCLC diagnosed in 2004-2011 from the National Cancer Database (NCDB).[8, 9] The authors concluded that adjuvant RT did not provide survival benefit in any disease stage and was even associated with decreased survival in early stage disease; adjuvant chemotherapy improved survival irrespective of stage, and adjuvant CRT was only associated with improved survival in stage IIA/IIB and IIIA disease.[8, 9] Both of these studies raised concerns of selection bias and confounding by indication[8, 9], which were adjusted for in one study only.[9]

A population-based study with recent real-world data could overcome some of the current shortcomings related to small patient numbers and lack of proper adjustment for confounders. Therefore, the primary aim of this population-based study was to compare OS between 4 different adjuvant treatment strategies in patients with stage I-III NSCLC who underwent an R1-2 resection. Secondary aims were to compare overall survival in 1:1 matched adjuvant treatment groups and to evaluate potential differences in treatment response among patient subgroups.

Material and methods

Our institutional review board approved this study (project number 18-377/C). The requirement to obtain informed consent was waived.

Study population

For this nationwide population-based observational cohort study, data from the Netherlands Cancer Registry (NCR) was used, wherein data on patient-, tumor- and treatment-related characteristics is stored. The NCR registers all newly diagnosed cancer cases based on notifications by the national automated pathological archive (PALGA). Diagnosis-therapy combination, the

national registry of hospital discharge diagnoses and radiotherapy institutions are additional sources. Trained data managers extract data from hospital records. Information on patients' vital status is updated through an annual linkage with the municipal personal records database.

Patients with NSCLC who were diagnosed between January 1st 2015 and December 31st 2018 and treated surgically were included. Exclusion criteria were cTis, cT0, cM1 stage, neoadjuvant treatment, radical surgical resection (R0), missing information on radicality of resection, a time interval from date of diagnosis to surgery $>$180 days, a time interval between surgery and adjuvant therapy of $>$75 days, pTNM stage IV disease and a second surgery with an R0 outcome. Finally, potential misleading overestimation of adjuvant therapy effect sizes through immortal time bias was mitigated using landmark analysis by excluding patients with a postoperative survival of $\leq$90 days.[10, 11] Irradical resection was defined as microscopic irradical resection (R1) or macroscopic irradical resection (R2). A procedure was classified as an R1 resection if the pathologist indicated that resection margins were involved, without a notification of irradicality by the surgeon in the operative report. A procedure was classified as an R2 resection when the surgeon mentioned residual disease in the operative report.

Patients were classified in four adjuvant treatment groups: 'no treatment', 'RT only', 'chemotherapy only' and 'chemo- and radiotherapy (CRT)'. To be allocated to the CRT group, both concurrent and sequential treatment were allowed. In case of sequential CRT, a maximum time frame of 5 months was chosen between the start of chemotherapy and the start of RT in case chemotherapy preceded RT (since 4 cycles of chemotherapy containing cisplatin every 3-4 weeks are generally recommended in the Netherlands, plus 4 weeks of recovery). A maximum time frame of 2 months was chosen between the end of RT and start of chemotherapy, considering recovery of possible acute toxicity. If the maximum time frame was exceeded, patients were classified as monotherapy in the category of treatment that was given first.

Variables

Studied variables included sex, age, WHO performance score, histology, differentiation grade, lateralization (left or right sided), tumor location (upper lobe, lower lobe and other [middle lobe, main bronchus or overlapping locations]), clinical T- and N-stage (8th edition of TNM), extent of surgery (sublobar [wedge or segmental resection], lobectomy/sleeve or bilobectomy/pneumonectomy), number of pathologic lymph nodes, pathologic T- and N-stage, and radicality of resection (R1 vs R2). For years in which data regarding cT- and pT-stage were only available according to the 7th edition (2015-2016), these variables were converted to cT- or pT-stage according to the 8th edition. For 71 patients with cT3 tumors and 65 patients with pT3 tumors this was not possible, so the cT and pT data were coded as missing. OS was defined as survival from date of surgical resection until death or last follow-up. The dataset was updated until March 2020.

Statistical analysis

Differences in categorical and continuous variables between patients in the 4 treatment groups were assessed with chi-square and one-way ANOVA tests, respectively. Missing data was considered to be 'missing at random' and handled by multiple imputation using chained equations, creating 20 new datasets.[12] Since for the purpose of subsequent weighting and matching steps only a single imputed dataset could be used, all subsequent analyses were performed with the one imputed dataset that in a multivariable Cox regression model for OS (including all studied variables) mostly reflected the same regression model in all 20 sets pooled.

Pretreatment imbalances between the 4 groups were expected and corrected for using propensity scores that were calculated based on all studied variables described above. Since more than 2 treatment groups are involved, generalized boosted regression modeling was ap-

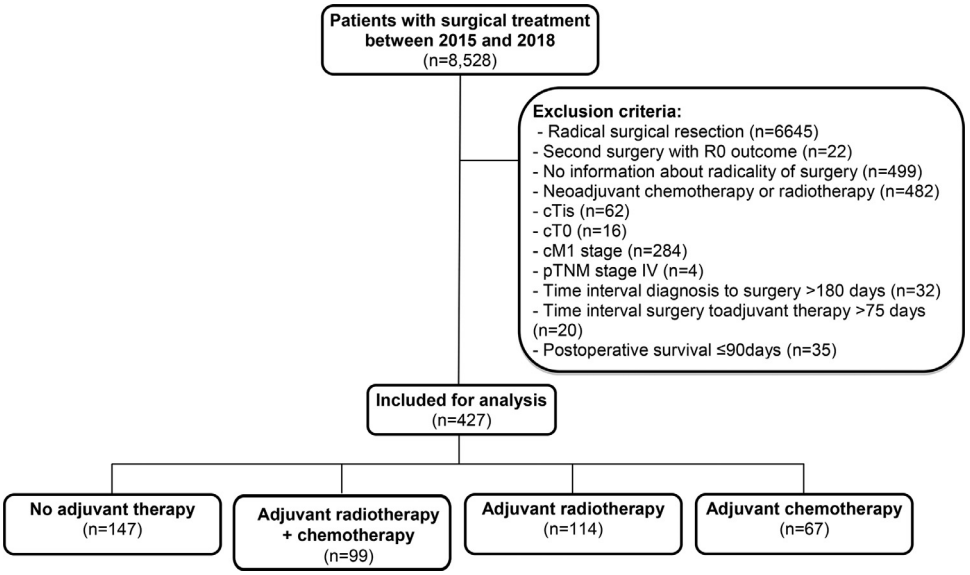

Fig. 1. Flowchart of patient inclusion. cM, clinical M stage; cT, clinical T stage; pTNM (version 8), pathologic tumor stage.

plied to estimate multinomial propensity scores.[13] The primary analysis is a 4-arm comparison that used these propensity scores to estimate the weights for a weighted Cox regression model studying the impact of the 4 different treatment arms on postoperative OS. For the secondary analyses, 2-arm comparisons were performed using 1:1 nearest-neighbor propensity score matching. Cohort A comprised matched analysis of chemotherapy (with or without RT) vs no chemotherapy (with or without RT), cohort B matched RT only vs no adjuvant therapy patients, and cohort C compared CRT to chemotherapy only. Kaplan-Meier and Cox regression analyses for OS were performed in each cohort.

Finally, interaction analyses were performed in abovementioned cohorts by entering interactions of patient- and tumor-related characteristics with the treatment group into Cox regression models, in order to explore whether in specific subgroups a certain treatment would have a differential effect on OS compared to other subgroups. Cox regression models provided hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed using SPSS version 25.0 (IBM Corp, IBM SPSS Statistics for Windows, Armonk, NY) and R version 3.6.3 ('mice', 'rms', 'twang', and 'MatchIt' packages). A p-value <0.05 was considered statistically significant.

Results

In total 8,528 patients were surgically treated for NSCLC, of whom 8,101 did not meet the inclusion criteria (Fig 1). Ultimately, 427 were eligible for analysis of whom 387 patients (90.6%) with an R1 resection and 40 (9.4%) with an R2 resection. In our final cohort, median follow-up was 22.6 months in all patients, and 30.9 months for patients alive at time of data collection. The mean age ($\pm$ SD) was 67.2 ($\pm$ 8.6) years and 246 patients (57.6%) were male. Adenocarcinoma and squamous cell carcinoma was seen in 194 (45.4%) and 199 (46.6%) patients, respectively. Information on baseline patient- and treatment-related characteristics are presented in Table 1.

Results of the multinomial propensity score-weighted Cox model demonstrated a significantly improved survival for the chemotherapy only and CRT groups (HR 0.41, 95%CI: 0.22-0.76; and HR 0.55, 95%CI: 0.37-0.81, respectively), compared to no adjuvant therapy (Table 2). No significant

Table 1
Baseline patient- and treatment-related characteristics of patients with R1-2 resection.

Characteristic	No adjuvant therapy (n = 147)	Adjuvant radiotherapy + chemotherapy (n = 99)	Only adjuvant radiotherapy (n = 114)	Only adjuvant chemotherapy (n = 67)	*p* value
Male gender	89 (60.5)	49 (49.5)	71 (62.3)	37 (55.2)	0.225
Age (y)[†]	69.0 ± 9.1	64.7 ± 8.4	68.3 ± 7.7	64.9 ± 8.2	<0.001[*]
WHO performance status					0.096
0	52 (61.9)	57 (68.7)	33 (43.4)	33 (68.8)	
1	29 (34.6)	24 (28.9)	40 (52.6)	12 (25.0)	
2	3 (3.6)	2 (2.4)	3 (3.9)	2 (4.2)	
3	0 (0)	0 (0)	0 (0)	1 (2.1)	
Unknown	63 (42.9)	16 (16.2)	38 (33.0)	19 (28.4)	
Tumor histology					0.169
Squamous cell ca	69 (46.9)	47 (47.5)	56 (49.1)	27 (40.3)	
Adenocarcinoma	70 (47.6)	47 (47.5)	43 (37.7)	34 (50.7)	
Other types	8 (5.4)	5 (5.1)	15 (13.2)	6 (9.0)	
Differentiation grade					0.042[*]
Well	6 (6.0)	0 (0)	0 (0)	0 (0)	
Moderate	65 (65.0)	43 (56.8)	49 (59.8)	30 (62.5)	
Poor/undifferentiated	29 (29.0)	34 (44.2)	33 (40.2)	18 (37.5)	
Unknown	47 (32.0)	22 (22.2)	32 (28.1)	19 (28.4)	
Lateralization					0.838
Left	68 (46.3)	50 (50.5)	58 (50.9)	31 (46.3)	
Tumor location					0.804
Main bronchus	3 (2.1)	6 (6.1)	2 (1.8)	3 (4.5)	
Upper lobe	73 (50.0)	53 (54.1)	59 (53.2)	37 (55.2)	
Middle lobe	12 (8.2)	5 (5.1)	5 (4.5)	4 (6.0)	
Lower lobe	50 (34.2)	28 (28.6)	41 (36.0)	19 (28.4)	
Overlapping	8 (5.5)	6 (6.1)	5 (4.5)	4 (6.0)	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	No adjuvant therapy (n = 147)	Adjuvant radiotherapy + chemotherapy (n = 99)	Only adjuvant radiotherapy (n = 114)	Only adjuvant chemotherapy (n = 67)	*p* value
Unknown	1 (0.7)	1 (1.0)	3 (2.6)	0 (0)	
Type of surgery[ǂ]					<0.001*
Wedge resection	19 (12.9)	0 (0)	4 (3.5)	2 (3.0)	
Segmental resection	5 (3.4)	1 (1.0)	0 (0)	0 (0)	
Lobectomy	87 (59.2)	60 (60.6)	78 (68.4)	39 (58.2)	
Bilobectomy	8 (5.4)	10 (10.1)	12 (10.5)	8 (11.9)	
Sleeve lobectomy	8 (5.4)	13 (13.1)	2 (1.8)	1 (1.5)	
Pneumonectomy	20 (13.6)	15 (15.2)	18 (15.8)	17 (25.4)	
Unknown/other	0 (0)	1 (1.1)	0 (0)	0 (0)	
Number of positive lymphnodes[§]	0 (0-1)	1 (0-2)	1 (0-2)	1 (0-2)	0.035
Pathologic T-stage					0.023*
pT1	38 (29.2)	8 (9.4)	15 (16.3)	9 (15.0)	
pT2	41 (31.5)	25 (29.4)	25 (27.2)	16 (26.7)	
pT3	25 (19.2)	27 (31.8)	24 (26.1)	17 (28.3)	
pT4	26 (20.0)	25 (29.4)	28 (30.4)	18 (30.0)	
Unknown	17 (11.6)	14 (14.1)	22 (19.3)	7 (10.4)	
Pathologic N-stage					<0.001*
pN0	91 (65.9)	27 (27.6)	49 (44.1)	16 (24.2)	
pN1	28 (20.3)	41 (41.8)	44 (39.6)	30 (45.5)	
pN2	18 (13.0)	30 (30.6)	18 (16.2)	20 (30.3)	
Unknown	9 (6.1)	1 (1.0)	3 (2.6)	1 (1.5)	

Data are presented as numbers with percentages in parentheses. In case of missing values, data are presented as valid percent, with the percentage of missings mentioned additionally.

* Significant difference ($p < 0.05$).

† Expressed as mean ± SD.

ǂ In case of multiple surgeries: type of initial surgery.

§ Expressed as median with interquartile range.

Table 2
Multinomial propensity score-weighted† Cox proportional hazard analysis for overall survival.

Adjuvant treatment	HR	95% CI	*p* value
None	Ref	-	-
Radiotherapy only	1.04	0.73-1.50	0.816
Chemotherapy only	0.41	0.22-0.76	0.005*
Chemotherapy and radiotherapy	0.55	0.37-0.81	0.003*

CI: confidence interval. HR: Hazard ratio.
* Statistically significant ($p < 0.05$).
† Multinomial propensity scores and weights were based on age, sex, WHO performance status, incidence year, tumor location, lateralization, histologic tumor type, differentiation grade, cTN-stage, pTN-stage, extent of surgery, and R2 vs R1 resection.

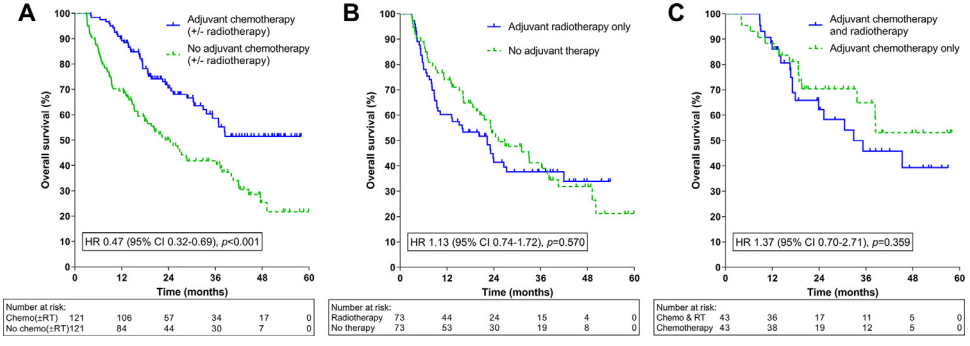

Fig. 2. Kaplan-Meier plots for postoperative overall survival of matched cohorts of patients who respectively received adjuvant chemotherapy (+/- radiotherapy) vs no adjuvant chemotherapy (+/- radiotherapy) (a), adjuvant radiotherapy only vs no adjuvant therapy (b) and adjuvant chemotherapy and radiotherapy vs adjuvant chemotherapy only (c).

difference in survival was found after RT only compared to no adjuvant therapy (HR 1.04, 95%CI: 0.73-1.50).

For our secondary analysis, propensity score matching resulted in well-balanced groups in all three cohorts (Table A.1). Cohort A, B, and C, consisted of 242, 146, and 86 matched patients, respectively (Fig 2). In cohort A, chemotherapy (+/- RT) significantly improved survival compared to omission of chemotherapy (+/- RT) (HR 0.47, 95%CI 0.32-0.69, $P < 0.001$). Cohort B showed that adjuvant RT did not improve OS compared to no adjuvant therapy (HR 1.13, 95%CI 0.74-1.72, $P = 0.570$). In cohort C, the addition of RT to chemotherapy only did not improve survival (HR 1.37, 95%CI 0.70-2.71, $P = 0.359$).

The results of subgroup analyses are demonstrated in Forest plots (Fig 3). In general, most clinical parameters were not significantly interacting with the influence of treatment on OS (interaction $p > 0.05$). In cohort A, chemotherapy improved OS in patients with lymph node metastases, especially in pN2 compared to pN0 patients (HR 0.19 vs 0.87, respectively; interaction $p = 0.005$). In cohort B, the effect of RT only compared to no therapy was significantly different in poor vs good/moderate differentiation grade (HR 1.79 vs 0.62, respectively; interaction $p = 0.016$). Although survival for radiotherapy after R2 resections seemed improved, this did not reach significance, possibly because of a small sample size. In cohort C, there was no subgroup with a significantly different outcome.

Discussion

Patients with stage I-III NSCLC who underwent an irradical (R1-R2) resection have a worse prognosis than those with a radical resection.[2, 3, 14-18] In order to potentially increase survival

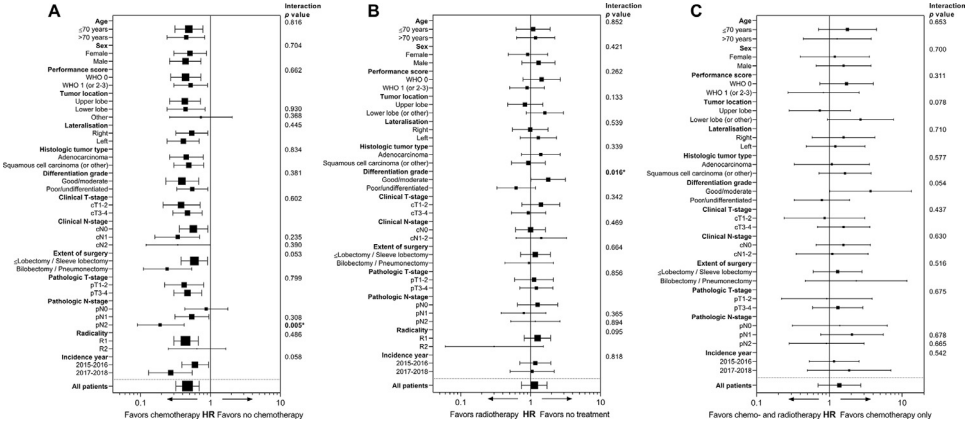

Fig. 3. Forest plots displaying subgroup analyses for postoperative overall survival in matched cohorts of patients who respectively received adjuvant chemotherapy (+/- radiotherapy) vs no adjuvant chemotherapy (+/- radiotherapy) (a), adjuvant radiotherapy only vs no adjuvant therapy (b) and adjuvant chemotherapy and radiotherapy vs adjuvant chemotherapy only (c).

after irradical resection, one could opt for adjuvant therapy. Our analyses in a real-world contemporary cohort of 427 patients show that adjuvant RT after an irradical resection did not significantly improve survival. This would indicate that (even modern) RT targeting residual disease does not suffice to increase survival for these patients. However, adjuvant chemotherapy did demonstrate a significant survival benefit. Adjuvant CRT improved survival compared to omitting adjuvant therapy, but compared to chemotherapy only, adding RT did not improve survival.

A search for possible interactions showed few subgroups with specific survival advantages or disadvantages in each treatment group. However, these subgroup analyses should be interpreted with caution as some subgroups had small sample sizes. Of notice is the interaction between pN-status and chemotherapy. Higher survival rates were found for chemotherapy in patients with lymph node metastases, especially in case of pN2 disease, whereas no significant advantage for pN0 patients could be observed. Regarding RT, the only subgroup with a significantly different survival compared to no adjuvant therapy were patients with a tumor of good/moderate differentiation grade. However, this potential survival difference for RT did not remain in the context of chemotherapy. A trend towards better survival with radiotherapy after R2 resections did not reach significance, perhaps due to a small sample size. Furthermore, no significant differences in survival were seen for chemoradiotherapy vs chemotherapy in subgroups.

Ideally, an irradical resection is prevented by means of a proper selection for surgery or different first line treatment. Recently, an internationally validated nomogram was presented that could aid in proper selection by providing the ability to predict the individual chance of an irradical resection in patients with stage I-III NSCLC planned for surgery.[19] In case an irradical resection still occurs, critical consideration of adjuvant treatment is warranted. Adjuvant RT after an irradical resection should be considered in stage I-II disease according to the ESMO Clinical Practice Guideline[20] and the current ASTRO clinical practice guideline states that patients with R1 or R2 disease may be appropriate candidates for postoperative radiotherapy, given either concurrently or sequentially with chemotherapy[21]. However, many studies investigating adjuvant RT are retrospective, have limited patient numbers and chemotherapy is variably used, which impedes firm conclusions. An early systematic review from the UK regarding adjuvant RT after R1 resections included 13 papers and concluded that there was no convincing evidence for a survival advantage for RT in patients who were not selected for re-resection.[22] Two recent aforementioned retrospective studies using NCDB data, found a detrimental effect of adjuvant RT on survival in pT1-2N0 disease and no survival benefit for RT in any disease stage.[8,9]

The definition for R1-2 resections in the current study is based on the national coding of resections by the Netherlands Cancer Registry and it encompasses involved resection margins. Other known criteria were not taken into account (e.g. regional lymph node metastases that were not removed, extracapsular extension of tumor in nodes removed separately or those at the margin of the primary lung specimen and positive cytology of pleural or pericardial effusions).[23] Other studies report on adjuvant radiotherapy in general, after R1-2 resections or pN2 stage. These studies are therefore less generalizable to patients with R1-2. A recent review on the role of adjuvant RT in NSCLC included 17 trials and concluded that adjuvant RT could be contemplated in patients with R1-2 resections or ypN2 disease after induction chemotherapy.[5] However, the supporting evidence and the reported clinical results are mostly based on small retrospective studies.[5] Regarding the effect of postoperative radiotherapy in N2 disease, recently the primary end-point analysis of the LungART study was presented, showing no statistically significant difference in 3-year disease-free survival for postoperative radiotherapy among stage IIIA N2 patients, following complete (R0) resection and after (neo) adjuvant chemotherapy.[24] An ongoing German RCT of interest (PORTAF) investigates whether accelerated adjuvant RT improves locoregional control compared to conventionally fractionated RT in patients with pN2 disease or after R1-R2 resections.[25] A possible explanation for the lack of benefit of adjuvant RT is that most failures are distant rather than locoregional.[26] Our study further underlines the limited role of radiotherapy after an irradical resection.

Regarding the role of adjuvant CRT after resection, in the prospective trial from 1994[7], patients with stage I-III disease and positive margins or an involved highest sampled paratracheal node were randomized between RT alone or CRT. RT was given in a split course of twice 20 Gy in five fractions with a three-week interval. A longer recurrence-free survival after CRT compared to RT was observed (median 20 vs 13 months, respectively; p=0.004).[7] In the two large NCDB studies[8, 9], adjuvant chemotherapy after irradical resection was associated with improved survival in tumor stage IA-III and IB-III, respectively, and adjuvant CRT was associated with improved survival in stage II and III patients, but not in stage I patients. In addition, no difference in 5-year survival was found for sequential vs concurrent therapy, nor for chemotherapy first vs RT first.[9] Two more recent retrospective American studies that used NCDB data in respectively 277 and 1,446 patients with an R1-2 resection, also found no significant differences in OS regarding sequential vs concurrent therapy and for the order of chemotherapy and RT.[27,28] Therefore, in general the findings of the current study regarding adjuvant chemotherapy and CRT are consistent with literature.

Since evidence for efficacy of adjuvant therapy after an irradical resection is scarce, knowledge on what actually happens in clinical practice is of interest. A survey among 768 medical and radiation oncologists in 41 European countries with questions regarding the use of adjuvant chemotherapy and RT in case of R1 resections demonstrated that adjuvant chemotherapy was recommended by 91.4% of participants, especially in higher tumor stages.[29] Moreover, 85% declared to discuss the limited clinical evidence of adjuvant treatments with patients.[29] Adjuvant RT was recommended by 48% and the most commonly used fractionation regimen was 60 Gy in 30 fractions.[29]

Limitations of the current study include the retrospective and observational nature. However, the rarity of irradical resections makes it difficult to run prospective trials with sufficient patient numbers. Also, we did not have information about local control, disease free survival or quality of life, whilst these can be important outcome measures as well in this setting. Another limitation is the absence of information regarding the use of immunotherapy. Since immunotherapy is upcoming in more recent years and solely used in a select group of NSCLC patients, it is not to be expected that many of the patients in our cohort were treated with immunotherapy. The study was strengthened by the use of a large and contemporary national database, comprising all NSCLC patients that were diagnosed over a 4-year period. Although residual confounding could not be excluded, another strength of this study included the adjustment for known confounders using appropriate statistical methods.

Conclusion

In conclusion, this population-based cohort study supports evidence for improved survival with adjuvant chemotherapy after an irradical resection for stage I-III NSCLC. Adjuvant RT did not improve OS compared to omission of adjuvant therapy or chemotherapy only, and a possible survival benefit in subgroups also could not be found. As systemic (and not local) therapy appears to benefit patients with an irradical resection, investigating the role of new systemic treatment strategies (e.g. targeted therapy, immunotherapy) is desired.[30, 31]

Conflict of interest

None.

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Supplementary materials

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