Trends in Postoperative Intensity-Modulated Radiation Therapy Use and Its Association With Survival Among Patients With Incompletely Resected Non–Small Cell Lung Cancer

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Abstract

IMPORTANCE National guidelines allow consideration of postoperative radiation therapy (PORT) among patients with incompletely resected non–small cell lung cancer (NSCLC). However, there is a paucity of prospective data because recently completed trials excluded patients with positive surgical margins. In addition, unlike for locally advanced NSCLC, the role of intensity-modulated radiation therapy (IMRT) for PORT remains unclear.

OBJECTIVE To evaluate trends of IMRT use for PORT in the US and the association of IMRT with survival outcomes among patients with incompletely resected NSCLC.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used data from the National Cancer Database for patients diagnosed between January 2004 and December 2019 with incompletely resected NSCLC who underwent upfront surgery with positive surgical margins followed by PORT.

EXPOSURES IMRT vs 3D conformal radiation therapy (3DCRT) for PORT.

MAIN OUTCOMES AND MEASURES The main outcome was overall survival. Multivariable Cox proportional hazards regression assessed the association of IMRT vs 3DCRT with overall survival. Multivariable logistic regression identified variables associated with IMRT. Propensity score matching (1:1) was performed based on variables of interest.

RESULTS A total of 4483 patients (2439 men [54.4%]; median age, 67 years [IQR, 60-73 years]) were included in the analysis. Of those, 2116 (47.2%) underwent 3DCRT and 2367 (52.8%) underwent IMRT. Median follow-up was 48.5 months (IQR, 31.1-77.2 months). The proportion of patients who underwent IMRT increased from 14.3% (13 of 91 patients) in 2004 to 70.7% (33 of 471 patients) in 2019 (P < .001). IMRT was associated with improved overall survival compared with 3DCRT (adjusted hazard ratio, 0.84; 95% CI, 0.78-0.91; P < .001). Similar findings were observed for 1463 propensity score–matched pairs; IMRT was associated with improved 5-year overall survival compared with 3DCRT (37.3% vs 32.2%; hazard ratio, 0.88; 95% CI, 0.80-0.96; P = .003). IMRT use was associated with receipt of treatment at an academic facility (adjusted odds ratio [aOR], 1.15; 95% CI, 1.00-1.33; P = .049), having T4 stage tumors (aOR, 1.50; 95% CI, 1.13-1.99; P = .005) or N2 or N3 stage tumors (aOR, 1.25; 95% CI, 1.04-1.51; P = .02), and receipt of pneumonectomy (aOR, 1.35; 95% CI, 1.02-1.80; P = .04).

CONCLUSION AND RELEVANCE This cohort study found that use of IMRT for PORT among patients with incompletely resected NSCLC increased in the US from 2004 to 2019 and was associated with improved survival compared with 3D conformal therapy.

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Abstract (continued)
improved survival compared with 3DCRT. Further studies are warranted to investigate the role of
different radiation therapy techniques for PORT.

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Introduction

Positive margins after resection for non–small cell lung cancer (NSCLC) are associated with a poor
prognosis and worse survival outcomes.¹ This problem persists despite substantial advances in
systemic therapy agents. For instance, the CheckMate 816 trial of neoadjuvant nivolumab and
chemotherapy for resectable NSCLC reported a 14% positive margin rate.² The National
Comprehensive Cancer Network guideline allows consideration of postoperative radiation therapy
(PORT) among patients with incompletely resected NSCLC.³ The recently reported LungART and
PORT-C trials excluded patients with positive margins.⁴,⁵

Prior analysis of the National Cancer Database (NCDB) showed an overall survival (OS) benefit
associated with PORT but did not compare the impact of radiation techniques.⁶ The role of IMRT for
PORT remains unclear. To address this knowledge gap, we performed a cohort study using a national
clinical oncology database to assess the trend of IMRT use in the US and its association with OS
compared with 3D conformal radiation therapy (3D CRT) among patients with incompletely
resected NSCLC.

Methods

This cohort study was performed under a protocol approved by the Roswell Park Comprehensive
Cancer Center, with a waiver of informed consent because the research met the criteria for minimal
risk to study participants. The study followed the Strengthening the Reporting of Observational
Studies in Epidemiology (STROBE) reporting guideline.

The NCDB was queried for patients diagnosed between January 2004 and December 2019 with
nonmetastatic NSCLC who underwent surgery with positive margins followed by either IMRT or
3DCRT for PORT. Variables of interest included facility type, age, race, insurance type, income,⁷
Charlson-Deyo comorbidity score, year of diagnosis, histologic features, tumor grade, T and N stage,
surgery, surgical margin, radiation therapy, and chemotherapy. Race was self-reported during the
initial assessment and was included to evaluate whether racial differences exist in undergoing IMRT.
All missing values were coded as unknown. Clinically pertinent variables, including medical
comorbidities, performance status, type and duration of systemic therapy, toxic effect profile, tumor
recurrence, and lung cancer–specific mortality, were not captured in the NCDB.

Statistical Analysis

The primary end points were OS, defined as the time between diagnosis and the last follow-up or
death. Baseline characteristics between the 3DCRT and IMRT arms were compared using Fisher exact
test or Mann-Whitney U test as appropriate. Cochran-Armitage test was performed to evaluate the
temporal trend of IMRT from 2004 to 2019. Kaplan-Meier method, log-rank test, and multivariable
Cox proportional hazards regression analysis were performed to evaluate the association of IMRT
with OS compared with 3D CRT. Interaction term analysis was performed to evaluate the
heterogeneous association of IMRT with OS. Survival data for patients diagnosed with NSCLC in 2019
were not captured in the NCDB, and these patients were not included for analysis of OS.
Multivariable logistic regression analysis was performed to identify variables associated with IMRT.
These models included the aforementioned clinically relevant variables.
Table 1. Baseline Characteristics of Patients With Incompletely Resected Non–Small Cell Lung Cancer Who Received IMRT or 3DCRT for Postoperative Radiation Therapy

| Variable                        | Before propensity score matching | After propensity score matching |
|---------------------------------|----------------------------------|---------------------------------|
|                                 | 3DCRT (n = 2116) | IMRT (n = 2367) | P value | 3DCRT (n = 1463) | IMRT (n = 1463) | P value |
| Patient characteristics         |                                |                          |         |                  |                  |         |
| Treatment facility type         |                                |                          |         |                  |                  |         |
| Nonacademic                     | 1553 (73.4)                   | 1649 (69.7)               | .01     | 1044 (71.4)      | 1052 (71.9)     | .96     |
| Academic                        | 542 (25.6)                    | 699 (29.5)                |         | 407 (27.8)       | 399 (27.3)      |         |
| Not available                   | 21 (1.0)                      | 19 (0.8)                  |         | 12 (0.8)         | 12 (0.8)        |         |
| Age, y                          |                                |                          |         |                  |                  |         |
| <65                             | 894 (42.2)                    | 940 (39.7)                | .09     | 617 (42.2)       | 630 (43.1)      | .65     |
| ≥65                             | 1222 (57.8)                   | 1427 (60.3)               |         | 846 (57.8)       | 833 (56.9)      |         |
| Sex                             |                                |                          |         |                  |                  |         |
| Female                          | 954 (45.1)                    | 1090 (46.0)               | .53     | 673 (46.0)       | 675 (46.1)      | .97     |
| Male                            | 1162 (54.9)                   | 1277 (54.0)               |         | 790 (54.0)       | 788 (53.9)      |         |
| Year of diagnosis, median (IQR) | 2012 (2009-2016)              | 2015 (2012-2018)          | <.001   | 2013 (2010-2016) | 2013 (2010-2016) | .65     |
| Race                            |                                |                          |         |                  |                  |         |
| Black                           | 210 (9.9)                     | 212 (9.0)                 | .01     | 145 (9.9)        | 133 (9.1)       | .78     |
| White                           | 1864 (88.1)                   | 2071 (87.5)               |         | 1284 (87.8)      | 1293 (88.4)     |         |
| Othera                          | 37 (1.7)                      | 75 (3.2)                  |         | 31 (2.1)         | 32 (2.2)        |         |
| Not available                   | 5 (0.2)                       | 9 (0.4)                   |         | 3 (0.2)          | 5 (0.3)         |         |
| Insurance type                  |                                |                          |         |                  |                  |         |
| Not insured                     | 44 (2.1)                      | 37 (1.6)                  | .34     | 30 (2.1)         | 27 (1.8)        | .99     |
| Governmentb                     | 1422 (67.2)                   | 1637 (69.2)               |         | 972 (66.4)       | 777 (66.8)      |         |
| Private                         | 636 (30.1)                    | 675 (28.5)                |         | 450 (30.8)       | 448 (30.6)      |         |
| Not available                   | 14 (0.7)                      | 18 (0.8)                  |         | 11 (0.8)         | 11 (0.8)        |         |
| Incomec                         |                                |                          |         |                  |                  |         |
| Above median                    | 973 (46.0)                    | 1105 (46.7)               | .01     | 677 (46.3)       | 680 (46.5)      | .95     |
| Below median                    | 890 (42.1)                    | 918 (38.8)                |         | 592 (40.5)       | 595 (40.7)      |         |
| Not available                   | 253 (12.0)                    | 344 (14.5)                |         | 194 (13.3)       | 188 (12.9)      |         |
| Charlson-Deyo comorbidity score |                                |                          |         |                  |                  |         |
| 0 or 1                          | 1759 (83.1)                   | 1962 (82.9)               | .84     | 1217 (83.2)      | 1211 (82.8)     | .81     |
| >1                              | 357 (16.9)                    | 405 (17.1)                |         | 246 (16.8)       | 252 (17.2)      |         |
| Tumor characteristics           |                                |                          |         |                  |                  |         |
| Site                            |                                |                          |         |                  |                  |         |
| Upper lobe                      | 1253 (59.2)                   | 1348 (56.9)               | .11     | 851 (58.2)       | 852 (58.2)      | .98     |
| Middle lobe                     | 93 (4.4)                      | 124 (5.2)                 |         | 64 (4.4)         | 68 (4.6)        |         |
| Lower lobe                      | 522 (24.7)                    | 641 (27.1)                |         | 376 (25.7)       | 374 (25.6)      |         |
| Other                           | 248 (11.7)                    | 254 (10.7)                |         | 172 (11.8)       | 169 (11.6)      |         |
| Side                            |                                |                          |         |                  |                  |         |
| Right                           | 1129 (53.4)                   | 1244 (52.6)               | .07     | 778 (53.2)       | 782 (53.5)      | .99     |
| Left                            | 859 (40.6)                    | 1012 (42.8)               |         | 606 (41.4)       | 603 (41.2)      |         |
| Other                           | 128 (6.0)                     | 111 (4.7)                 |         | 79 (5.4)         | 78 (5.3)        |         |
| Gradea                          |                                |                          | <.001   | 76 (5.2)         | 66 (4.5)        | .71     |
| I                               | 90 (4.3)                      | 103 (4.4)                 |         | 486 (33.2)       | 490 (33.5)      |         |
| II                              | 675 (31.9)                    | 623 (26.3)                |         | 571 (39.0)       | 554 (37.9)      |         |
| III                             | 825 (39.0)                    | 726 (30.7)                |         | 29 (2.0)         | 36 (2.5)        |         |
| IV                              | 47 (2.2)                      | 38 (1.6)                  |         | 301 (20.6)       | 317 (21.7)      |         |
| Not available                   | 479 (22.6)                    | 877 (37.1)                |         |                  |                  |         |
| Histologic features             |                                |                          |         |                  |                  |         |
| Squamous                        | 881 (41.6)                    | 903 (38.1)                | .02     | 589 (40.3)       | 600 (41.0)      | .71     |
| Nonsquamous                      | 1235 (58.4)                   | 1464 (61.9)               |         | 874 (59.7)       | 863 (59.0)      |         |

(continued)
To reduce selection bias, propensity score matching was performed based on all variables of interest. Matching was performed using a nearest-neighbor method in a 1:1 ratio without replacements. The standardized differences of all variables were lower than 0.1, indicating adequate match. To exclude patients who died after surgery, sensitivity analysis was performed by repeating the multivariable Cox proportional hazards regression analysis among patients with postdiagnosis survival of more than 4 months. In addition, patients included in our study were diagnosed over the span of more than a decade with different American Joint Committee on Cancer (AJCC) Cancer Staging Manual editions, which may have led to misclassification in staging for select patients. Multivariable Cox proportional hazards regression was also repeated among patients diagnosed based on the AJCC Cancer Staging Manual, Seventh Edition only.

All P values were 2-sided, and P < .05 was considered statistically significant. Analyses were performed using R, version 4.0.3 (R Project for Statistical Computing).

Table 1. Baseline Characteristics of Patients With Incompletely Resected Non–Small Cell Lung Cancer Who Received IMRT or 3DCRT for Postoperative Radiation Therapy (continued)

| Variable | Before propensity score matching | After propensity score matching |
|----------|---------------------------------|---------------------------------|
|          | Patients, No. (%) | Patients, No. (%) | P value |
|          | 3DCRT (n = 2116) | IMRT (n = 2367) | 3DCRT (n = 1463) | IMRT (n = 1463) | P value |
| T stage  |                   |                   |                   |                   | |
| 1        | 267 (12.6)        | 246 (10.4)        | 200 (13.7)        | 186 (12.7)        | .94     |
| 2        | 512 (24.2)        | 474 (20.0)        | 369 (25.2)        | 369 (25.2)        | .94     |
| 3        | 496 (23.4)        | 499 (21.1)        | 370 (25.3)        | 383 (26.2)        | .94     |
| 4        | 191 (9.0)         | 238 (10.1)        | 153 (10.5)        | 156 (10.7)        | .94     |
| Not available | 650 (30.7) | 910 (38.4)        | 371 (25.4)        | 369 (25.2)        | .94     |
| N stage  |                   |                   |                   |                   | |
| 0 or 1   | 1036 (49.0)       | 946 (40.0)        | 747 (51.1)        | 761 (52.0)        | .83     |
| 2 or 3   | 325 (15.4)        | 398 (16.8)        | 263 (18.0)        | 252 (17.2)        | .83     |
| Not available | 755 (35.7) | 1023 (43.2)       | 453 (31.0)        | 450 (30.8)        | .83     |
| Treatment |                   |                   |                   |                   | |
| Chemotherapy |                   |                   |                   |                   | |
| None     | 512 (24.2)        | 476 (20.1)        | 322 (22.0)        | 327 (22.4)        | .94     |
| Single agent | 90 (4.3) | 86 (3.6)         | 59 (4.0)          | 54 (3.7)          | .94     |
| Multiple agents | 1298 (61.3) | 1573 (66.5) | 937 (64.0)        | 931 (63.6)        | .94     |
| Other    | 216 (10.2)        | 232 (9.8)         | 145 (9.9)         | 151 (10.3)        | .94     |
| Surgery  |                   |                   |                   |                   | |
| Sublobar resection | 604 (28.5) | 646 (27.3)     | 414 (28.3)        | 423 (28.9)        | .93     |
| Lobectomy | 1190 (56.2) | 1361 (57.3) | 829 (56.7)        | 812 (55.5)        | .93     |
| Pneumonectomy | 139 (6.6) | 179 (7.6)      | 103 (7.0)         | 105 (7.2)         | .93     |
| Other    | 183 (8.6)         | 181 (7.6)         | 117 (8.0)         | 123 (8.4)         | .93     |
| Surgical margin |       |                   |                   |                   | |
| Other    | 771 (36.4)        | 951 (40.2)        | 547 (37.4)        | 549 (37.5)        | .99     |
| Microscopic | 1110 (52.5) | 1194 (50.4) | 763 (52.2)        | 763 (52.2)        | .99     |
| Macroscopic | 235 (11.1) | 222 (9.4)      | 153 (10.5)        | 151 (10.3)        | .99     |

Abbreviations: 3DCRT, 3D conformal radiation therapy; IMRT, intensity modulated radiation therapy.

a “Other” includes, but is not limited to, American Indian, Asian, and Pacific Islander. They were grouped together because the sample size of each subgroup was too small for analysis.

b Includes Medicaid and Medicare.
Results

A total of 4483 patients (2439 men [54.4%]; median age, 67 years [IQR, 60-73 years]) met our inclusion criteria (Table 1). Of those, 2116 (47.2%) underwent 3DCRT and 2367 (52.8%) underwent IMRT. Median follow-up was 48.5 months (IQR, 31.1-77.2 months). The proportion of patients who underwent IMRT increased from 14.3% (13 of 91 patients) in 2004 to 70.7% (333 of 471 patients) in 2019 (P < .001) (Figure 1).

On multivariable Cox proportional hazards regression, IMRT was associated with improved OS compared with 3DCRT (5-year OS, 38.2% vs 31.9%; adjusted hazard ratio [aHR], 0.84; 95% CI, 0.78-0.91; P < .001). Having nonsquamous tumors (aHR, 0.87; 95% CI, 0.81-0.95; P = .001) and receipt of a recent diagnosis (aHR, 0.98; 95% CI, 0.97-0.99; P < .001), lobectomy (aHR, 0.87; 95% CI, 0.79-0.96; P = .007), multi-agent chemotherapy (aHR, 0.81; 95% CI, 0.73-0.89; P < .001), and treatment at an academic facility (aHR, 0.81; 95% CI, 0.74-0.88; P < .001) were associated with improved OS (Table 2). Age 65 years or older, male sex, worse comorbidities, and presence of grade 3 tumors, T3 and T4 stage tumors, and N2 and N3 stage tumors were associated with worse OS (Table 2). There was no statistically significant interaction with T stage (interaction P = .86) or N stage (interaction P = .57), surgical margin status (interaction P = .35), or histologic features (interaction P = .93).

After propensity score matching, 1463 matched pairs were identified. All variables were well balanced (Table 1). Compared with 3DCRT, IMRT was associated with improved 5-year OS (37.3% vs 32.2%; HR, 0.88; 95% CI, 0.80-0.96; P = .003) (Figure 2).

On multivariable logistic regression analysis (Table 2), patients were more likely to receive IMRT if they had received a recent diagnosis of NSCLC (adjusted odds ratio [aOR], 1.17; 95% CI, 1.15-1.19; P < .001), had nonsquamous tumors (aOR, 1.15; 95% CI, 1.01-1.32; P = .04), received treatment at an academic facility (aOR, 1.15; 95% CI, 1.00-1.33; P = .049), underwent pneumonectomy (aOR, 1.35; 95% CI, 1.02-1.80; P = .04), received multi-agent chemotherapy (aOR, 1.20; 95% CI, 1.02-1.42; P = .03), and had N2 or N3 stage tumors (aOR, 1.25; 95% CI, 1.04-1.51; P = .02) and T4 stage tumors (aOR, 1.50; 95% CI, 1.13-1.99; P = .005). On sensitivity analysis, similar survival outcomes for IMRT were observed among 3883 patients (86.6%) with postdiagnosis survival of more than 4 months (aHR, 0.87; 95% CI, 0.80-0.95; P = .001) and among 2575 patients (57.4%) with staging based on the AJCC Cancer Staging Manual, Seventh Edition only (aHR, 0.82; 95% CI, 0.74-0.90; P < .001).

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**Figure 1. Trends in Use of Intensity-Modulated Radiation Therapy (IMRT) vs 3D Conformal Radiation Therapy (3DCRT) From January 2004 to December 2019**

![Graph showing trends in IMRT vs 3DCRT use from 2004 to 2019.](https://jamanetwork.com/)

Error bars represent 95% CIs.
Table 2. Multivariable Cox Proportional Hazards Regression and Logistic Regression Analyses for the Association of Variables With Overall Survival and Intensity-Modulated Radiation Therapy

| Variable                     | Cox proportional hazards regression | Logistic regression |                  |
|------------------------------|-------------------------------------|---------------------|------------------|
|                              | aHR (95% CI)                       | P value             | aOR (95% CI)     | P value |
| Patient characteristics      |                                     |                     |                  |
| Treatment facility type      |                                     |                     |                  |
| Nonacademic                  | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| Academic                     | 0.81 (0.74-0.88)                   | <.001               | 1.15 (1.00-1.33) | .049    |
| Age, y                       |                                     |                     |                  |
| <65                          | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| ≥65                          | 1.26 (1.14-1.39)                   | <.001               | 1.12 (0.96-1.31) | .16     |
| Sex                          |                                     |                     |                  |
| Female                       | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| Male                         | 1.18 (1.09-1.28)                   | <.001               | 0.95 (0.84-1.09) | .48     |
| Year of diagnosis            |                                     |                     |                  |
| For every 1-y increase       | 0.98 (0.97-0.99)                   | <.001               | 1.17 (1.15-1.19) | <.001   |
| Race                         |                                     |                     |                  |
| Black                        | 1.05 (0.91-1.20)                   | .50                 | 0.86 (0.69-1.07) | .19     |
| White                        | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| Othera                       | 0.72 (0.54-0.97)                   | .03                 | 1.53 (1.00-2.36) | .05     |
| Insurance type               |                                     |                     |                  |
| Not insured                  | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| Governmentb                  | 1.17 (0.85-1.61)                   | .32                 | 1.26 (0.78-2.04) | .35     |
| Private                      | 1.05 (0.77-1.44)                   | .77                 | 1.2 (0.75-1.94)  | .45     |
| Incomec                      |                                     |                     |                  |
| Above median                 | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| Below median                 | 0.98 (0.90-1.06)                   | .57                 | 0.95 (0.83-1.09) | .45     |
| Charlson-Deyo comorbidity score |                                 |                     |                  |
| 0 or 1                       | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| >1                           | 1.17 (1.06-1.29)                   | .002                | 1.01 (0.85-1.20) | .90     |
| Tumor characteristics        |                                     |                     |                  |
| Site                         |                                     |                     |                  |
| Upper lobe                   | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| Middle lobe                  | 1.00 (0.82-1.21)                   | .99                 | 1.32 (0.97-1.80) | .08     |
| Lower lobe                   | 1.15 (1.05-1.26)                   | .002                | 1.10 (0.95-1.28) | .21     |
| Other                        | 1.13 (0.96-1.32)                   | .14                 | 1.05 (0.80-1.37) | .72     |
| Side                         |                                     |                     |                  |
| Right                        | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| Left                         | 1.00 (0.92-1.09)                   | .96                 | 1.08 (0.95-1.24) | .24     |
| Other                        | 0.95 (0.75-1.19)                   | .64                 | 0.71 (0.49-1.04) | .08     |
| Gradec                       |                                     |                     |                  |
| I                            | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| II                           | 1.11 (0.92-1.34)                   | .28                 | 0.74 (0.53-1.02) | .07     |
| III                          | 1.32 (1.09-1.59)                   | .004                | 0.75 (0.54-1.04) | .08     |
| Other                        | 1.37 (1.01-1.87)                   | .04                 | 0.61 (0.35-1.06) | .08     |
| Histologic features          |                                     |                     |                  |
| Squamous                     | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| Nonsquamous                  | 0.87 (0.81-0.95)                   | .001                | 1.15 (1.01-1.32) | .04     |
| T stage                      |                                     |                     |                  |
| 1                            | 1.00 [Reference]                   | NA                  | 1.00 [Reference] | NA      |
| 2                            | 1.14 (1.00-1.30)                   | .06                 | 0.99 (0.78-1.24) | .91     |
| 3                            | 1.37 (1.19-1.57)                   | <.001               | 1.07 (0.85-1.35) | .56     |
| 4                            | 1.31 (1.11-1.54)                   | .001                | 1.50 (1.13-1.99) | .005    |

(continued)
To our knowledge, this is the first study using a nationwide clinical oncology database to report an OS benefit associated with IMRT compared with 3DCRT for PORT among patients with incompletely resected NSCLC. The survival benefit associated with IMRT in our study is consistent with prior literature of locally advanced NSCLC, suggesting that the survival benefit may in part be associated with lower pulmonary toxic effects and cardiac doses. Our finding of improved OS associated with IMRT is also consistent with results of the recently reported LungART and PORT-C trials, although both excluded patients with positive margins. The PORT-C trial used IMRT in 90% of patients and reported improved disease-free survival among per-protocol patients without any grade 4 or 5 toxic effects.

### Table 2. Multivariable Cox Proportional Hazards Regression and Logistic Regression Analyses for the Association of Variables With Overall Survival and Intensity-Modulated Radiation Therapy (continued)

| Variable        | Cox proportional hazards regression | Logistic regression |
|-----------------|-------------------------------------|---------------------|
|                 | aHR (95% CI)                         | aOR (95% CI)        |
|                 | P value                              | P value             |
| N stage         |                                     |                     |
| 0 or 1          | 1.00 [Reference]                     | 1.00 [Reference]    |
| 2 or 3          | 1.44 (1.30-1.60)                     | 1.25 (1.04-1.51)    |
| Treatment       |                                     |                     |
| Chemotherapy    |                                     |                     |
| None            | 1.00 [Reference]                     | 1.00 [Reference]    |
| Single agent    | 1.16 (0.95-1.41)                     | 1.13 (0.79-1.60)    |
| Multiple agents | 0.81 (0.73-0.89)                     | 1.20 (1.02-1.42)    |
| Other           | 1.09 (0.95-1.25)                     | 1.32 (1.04-1.69)    |
| Surgery         |                                     |                     |
| Sublobar resection | 1.00 [Reference]    | 1.00 [Reference]    |
| Lobectomy       | 0.87 (0.79-0.96)                     | 1.02 (0.87-1.20)    |
| Pneumonectomy   | 0.97 (0.81-1.15)                     | 1.35 (1.02-1.80)    |
| Other           | 1.58 (1.34-1.87)                     | 0.85 (0.65-1.12)    |
| Surgical margin |                                     |                     |
| Sublobar resection | 1.00 [Reference]    | 1.00 [Reference]    |
| Lobectomy       | 0.85 (0.78-0.92)                     | 0.88 (0.77-1.01)    |
| Pneumonectomy   | 1.04 (0.91-1.19)                     | 0.91 (0.73-1.15)    |

**Abbreviations:** aHR, adjusted hazard ratio; aOR, adjusted odds ratio.

* "Other" includes, but is not limited to, American Indian, Asian, and Pacific Islander. They were grouped together because the sample size of each subgroup was too small for analysis.

* Includes Medicaid and Medicare.

* Based on the median household income adjusted for 2016 inflation ($50353) in each patient’s zip code, according to 2016 American Community Survey data.

* Grade I indicates well differentiated tumor; II, moderately differentiated; III, poorly differentiated; and IV, undifferentiated.

### Figure 2. Cumulative Hazard of Overall Mortality Between Patients Who Received Intensity-Modulated Radiation Therapy (IMRT) vs 3D Conformal Radiation Therapy (3DCRT) After Propensity Score Matching

![Figure 2](https://jamanetwork.com/)

**Discussion**

To our knowledge, this is the first study using a nationwide clinical oncology database to report an OS benefit associated with IMRT compared with 3DCRT for PORT among patients with incompletely resected NSCLC. The survival benefit associated with IMRT in our study is consistent with prior literature of locally advanced NSCLC, suggesting that the survival benefit may in part be associated with lower pulmonary toxic effects and cardiac doses. Our finding of improved OS associated with IMRT is also consistent with results of the recently reported LungART and PORT-C trials, although both excluded patients with positive margins. The PORT-C trial used IMRT in 90% of patients and reported improved disease-free survival among per-protocol patients without any grade 4 or 5 toxic effects.
effects. The LungART trial, however, used IMRT in only 10% of patients and reported higher rates of cardiopulmonary toxic effects after PORT.

Because the bronchial stump has been shown to be the most common treatment failure site, with high mediastinal failure rates regardless of initial N stage, the National Comprehensive Cancer Network guideline recommends that the clinical target volume covers the postsurgical areas and high-risk draining lymph node stations. The extent and proximity of clinical target volume to organs at risk may also explain our findings that patients with higher tumor stage and those who underwent pneumonectomy were more likely to undergo IMRT as well as the increasing trend in IMRT use over time. Consistent with a prior study, the Cox proportional hazards regression analysis in our study found that IMRT was associated with improved OS regardless of stage of incompletely resected NSCLC.

Beyond IMRT, new methods of limiting the toxic effects of PORT continue to be explored. Proton therapy for PORT is associated with comparable oncologic outcomes and improved toxic effect profiles compared with IMRT. A prospective trial investigating postoperative stereotactic body radiation therapy is currently ongoing.

Limitations
This study has limitations, including the use of retrospective data. Although extracapsular extension was shown to be associated with worse survival, such high-risk features were not captured in the NCDB. In addition, performance status, cardiopulmonary toxic effect profiles, and tumor recurrence outcomes were also unavailable in the NCDB, and selection bias may have occurred despite multivariable analyses and propensity score matching. Furthermore, because all patients included in the cohort received a diagnosis of NSCLC before the publication of the CheckMate 816 trial, many of them did not receive immunotherapy. Our findings may need to be validated further based on a more recent patient cohort.

Conclusions
In this cohort study, use of IMRT for PORT among patients with incompletely resected NSCLC increased in the US from 2004 to 2019 and was associated with improved survival outcomes compared with 3DCRT. Further studies are warranted to investigate the role of IMRT for PORT.
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REFERENCES

1. Predina JD, Keating J, Patel N, Nims S, Singhal S. Clinical implications of positive margins following non–small cell lung cancer surgery. J Surg Oncol. 2016;113(3):264-269. doi:10.1002/jso.24130

2. Forde PM, Spicer J, Lu S, et al; CheckMate 816 Investigators. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med. 2022;386(21):1973-1985. doi:10.1056/NEJMoa2202170

3. National Comprehensive Cancer Network. Non–small cell lung cancer (version 3.2022). Accessed April 30, 2022. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

4. Hui Z, Men Y, Hu C, et al. Effect of postoperative radiotherapy for patients with PI1IA-N2 non-small cell lung cancer after complete resection and adjuvant chemotherapy: the phase 3 PORT-C randomized clinical trial. JAMA Oncol. 2021;7(8):1178-1185. doi:10.1001/jamaoncol.2021.1910

5. Le Pechoux C, Pourel N, Barlesi F, et al. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial. Lancet Oncol. 2022;23(1):104-114. doi:10.1016/S1470-2045(21)00606-9

6. Wang EH, Corso CD, Rutter CE, et al. Postoperative radiation therapy is associated with improved overall survival in incompletely resected stage II and III non–small-cell lung cancer. J Clin Oncol. 2015;33(25):2727-2734. doi:10.1200/JCO.2015.61.1517

7. US Census Bureau. American Community Survey. Accessed August 3, 2022. https://www.census.gov/acs/

8. Haukoos JS, Lewis RJ. The propensity score. JAMA. 2015;314(15):1637-1638. doi:10.1001/jama.2015.13480

9. Jegadeesh N, Liu Y, Gillespie T, et al. Evaluating intensity-modulated radiation therapy in locally advanced non-small-cell lung cancer: results from the National Cancer Data Base. Clin Lung Cancer. 2016;17(5):398-405. doi:10.1016/j.cllc.2016.01.007

10. Chun SG, Hu C, Choy H, 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. 2017;35(1):56-62. doi:10.1200/JCO.2016.69.1378

11. Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. Int J Radiat Oncol Biol Phys. 2006;65(4):1097-1105. doi:10.1016/j.ijrobp.2006.02.007

12. Berman AT, Teo BK, Dolney D, et al. An in-silico comparison of proton beam and IMRT for postoperative radiotherapy in completely resected stage IIIA non-small cell lung cancer. Radiat Oncol. 2013;8:144. doi:10.1186/1748-717X-8-144

13. Boyce-Fappiano D, Nguyen QN, Chapman BV, et al. Single institution experience of proton and photon-based postoperative radiation therapy for non–small-cell lung cancer. Clin Lung Cancer. 2021;22(5):e745-e755. doi:10.1016/j.cllc.2021.02.002

14. Remick JS, Schowenolf C, Gabriel P, et al. First clinical report of proton beam therapy for postoperative radiotherapy for non-small-cell lung cancer. Clin Lung Cancer. 2017;18(4):364-371. doi:10.1016/j.clcc.2016.12.009

15. Single fraction stereotactic body radiation therapy after surgery in treating patients with non–small cell lung cancer. ClinicalTrials.gov identifier: NCT04073745. Updated May 4, 2022. Accessed August 3, 2022. https://clinicaltrials.gov/ct2/show/NCT04073745

16. Olszyna-Seremeta M, Socha J, Wierchowski M, Kęplka L. Patterns of failure after postoperative radiotherapy for incompletely resected (R1) non-small cell lung cancer: implications for radiation target volume design. Lung Cancer. 2013;80(2):179-184. doi:10.1016/j.lungcan.2013.01.010