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No Survival Advantage of Intermediate Radiotherapy Dose Escalation in Stage III NSCLC Receiving Delayed Immunotherapy after Chemoradiation

Jinwoo Park[1]*, Minji Kim[1], Seung Lee[2]

[1]Department of Clinical Oncology and Cancer Medicine, College of Medicine, Seoul National University, Seoul, South Korea.

[2]Department of Precision Cancer Therapeutics, Faculty of Medical Sciences, KAIST, Daejeon, South Korea.

***E-mail** ✉ jinwoo.park@outlook.com

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ABSTRACT

Whether intensifying the radiotherapy dose for unresectable stage III NSCLC that is later managed with immunotherapy provides any advantage remains poorly understood. This analysis was designed to explore whether intermediate-dose escalation (IDE) yields a survival benefit in stage III NSCLC treated with definitive concurrent chemoradiation (dcCRT) and subsequent immunotherapy. The study extracted information from the National Cancer Database. All-cause mortality was evaluated through multivariable Cox regression, contrasting a standard RT dose (SD) (60 Gy ± 10%) against IDE (64–74 Gy). Within the pre-immunotherapy timeframe, 47,315 individuals were diagnosed and managed exclusively with dcCRT, while 4,947 received dcCRT in combination with immunotherapy. Among the dcCRT-only subset, SD was associated with a statistically significant increase in mortality but a clinically trivial difference compared with IDE (HR: 1.09, 95% CI: 1.07-1.12; P < 0.0001). During the immunotherapy period, SD remained associated with lower mortality than IDE (HR: 1.17, 95% CI: 1.03-1.33; P = 0.02). The survival benefit linked to IDE, however, applied exclusively to patients whose immunotherapy began within six weeks of completing RT (HR: 1.26, 95% CI: 1.05-1.6; P = 0.01). No mortality divergence emerged between SD and IDE for those starting immunotherapy at 7–10 weeks (HR: 1.13, 95% CI: 0.88-1.45; P = 0.35) nor for delays exceeding 10 weeks after RT completion (HR: 0.74, 95% CI: 0.51-1.07; P = 0.11). For stage III unresectable NSCLC patients who do not initiate immunotherapy more than 6 weeks after dcCRT, the IDE of RT is unwarranted.

Keywords: Chemoradiation, Chemotherapy, Immunotherapy, National cancer database, Non-small cell lung cancer, RT dose escalation

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Introduction

Cancer-related death in the United States is most frequently attributed to lung cancer [1]. Non-small cell lung cancer (NSCLC) constitutes over 85% of all lung cancer diagnoses [2]. Approximately one-third of NSCLC cases present at stage III, and 70% of these are deemed unresectable [3]. The 5-year survival rate among stage III NSCLC patients ranges from 15% to 30% [4].

The established historical approach for unresectable stage III NSCLC patients with preserved performance status involved platinum-doublet chemotherapy delivered concurrently with radiation—definitive concurrent chemoradiation (dcCRT) [5]. Despite achieving locoregional control in 60%–70% of instances, progression-free survival (PFS) and overall survival (OS) figures remain disheartening [6]. Before durvalumab became available, efforts focused on radiation dose escalation to bolster local control and OS in this population. The 60 Gy benchmark was established by the Radiation Therapy Oncology Group (RTOG) 7301 study and has remained unchanged since the 1970s [7]. A succession of investigations since then has sought to define the ideal RT dose for stage III NSCLC, on the premise that increasing the RT dose should translate into better local and regional

control and improved OS [4, 8-15]. Prospective research confirmed that exceeding 80 Gy is safe so long as conventional lung dose limits are honored with definitive RT alone, and transitioning from 60 Gy to 66 Gy with concurrent chemotherapy is safe. However, it does not produce a meaningful shift in overall survival [16, 17]. A large randomized phase III multi-institutional study, RTOG 0617, was launched before the immunotherapy era to test RT dose escalation (74 Gy) alongside chemotherapy with or without cetuximab, compared against the standard chemoradiotherapy dose (60 Gy) with or without cetuximab [9]. RTOG 0617 did not uncover any survival benefit for either the 74 Gy dose or the addition of cetuximab to the standard backbone [18, 19]. Defying expectations, the 74 Gy arm was associated with poorer OS than the 60 Gy arm [9]. The counterintuitive outcome spurred numerous investigators to propose explanations [8, 20, 21]. Potential drivers of the inferior OS observed with 74 Gy include elevated treatment-linked mortality, greater difficulty delivering the full concurrent chemotherapy course, and a higher incidence of non-compliant RT planning in the escalated dose cohort compared with the 60 Gy cohort [9]. Even after accounting for several of these variables, OS remained worse in the 74 Gy group [8]. A distinct concern with dose escalation is the potential for aggravated immunosuppression resulting from RT-induced depletion of immune cells at higher radiation doses [22, 23]. The ultimate recommendation was that 60 Gy remain the standard RT dose for unresectable stage III NSCLC, and that doses exceeding 74 Gy be avoided [9]. Critically, RTOG 0617 was designed to compare only two dose levels—74 Gy versus 60 Gy—and excluded patients treated at intermediate doses between those levels [9]. Consequently, the question of whether intermediate dose escalation (IDE) (from 64 to 74 Gy) yields any clinical value for individuals treated solely with dcCRT has remained open.

The relevance of IDE has intensified in modern oncology because the combination of dcCRT followed by durvalumab has become the standard treatment for unresectable stage III NSCLC, supported by the landmark PACIFIC trial, which assigned patients with good performance status after dcCRT to durvalumab or placebo [24, 25]. Adding adjuvant durvalumab to dcCRT was tied to improvements in both PFS and OS [24]. Although the PACIFIC trial showed notable survival gains, intrathoracic recurrences were still documented in 36% of participants, a pattern that might reflect the modest RT doses employed, since the majority received between 54 and 66 Gy [24]. A subsequent study, PACIFIC-R, an observational/non-interventional retrospective analysis, indicated that about half of real-world unresectable stage III NSCLC patients given the PACIFIC regimen actually received an RT dose exceeding 60 Gy. However, the report lacks granular dose details and does not link dose to survival outcomes [26]. This observation suggests that the community still lacks a definitive answer on the benefits of intermediate-dose escalation below the 74 Gy threshold. A small number of retrospective analyses have suggested that delivering higher-dose radiation (< 74 Gy) with chemotherapy, followed by durvalumab, is safe and yields toxicity profiles, local control, and distant control rates similar to those observed in the PACIFIC trial [27, 28]. In one report covering 39 stage III NSCLC patients treated with RT doses above 66 Gy concurrently with chemotherapy before durvalumab, the regimen appeared safe. It might enhance outcomes for carefully selected patients. The thoracic failure rate reached 21%, and the 12-month OS was 79%, whereas the PACIFIC trial reported a 38% thoracic failure rate and 81% 12-month OS [27]. A separate European analysis included 78 patients and compared RT doses of 73.5 Gy versus 66 Gy, both followed by durvalumab, and found no differences in local, regional, or distant control, concluding that RT dose escalation can be safely paired with durvalumab [28]. Of note, the 73.5 Gy higher dose was given alongside sequential chemotherapy, while the 66 Gy arm employed concurrent chemotherapy. Despite this, the question of whether the safe intermediate escalated dose actually translates into prolonged survival remains unresolved, owing to the modest sample sizes and inconsistent treatment regimens across studies. No prospective investigation has directly addressed the role of dose escalation—and specifically IDE—in affecting OS for unresectable stage III NSCLC in the period after durvalumab received approval and immunotherapy entered routine use.

The present study leverages the National Cancer Database (NCDB) to examine the relationship between IDE and OS in unresectable stage III NSCLC, both before and, crucially, after the immunotherapy era. We hypothesize that intermediate RT dose escalation, meaning up to 74 Gy, may be superfluous when concurrent chemoradiation is followed by immunotherapy for unresectable stage III NSCLC.

Materials and Methods

Data source

Information was obtained from the NCDB, a collaborative oncology outcomes platform that pools records from more than 1500 Commission on Cancer-accredited cancer programs spanning the United States and Puerto Rico. Functioning as a hospital-based registry drawing from multiple centers, it encompasses upwards of 70% of incident cancer cases documented annually across the nation through contributing hospital cancer registries. The reliance on de-identified records meant the protocol qualified for exemption from Institutional Review Board (IRB) evaluation.

Study population

The analysis included individuals aged 18 and above who underwent concurrent chemoradiation—defined as both modalities commencing within a 30-day window—and were found to have unresectable stage III NSCLC during the 2004–2020 period. Every participant received multi-agent chemotherapy. Cases were excluded if surgery had been performed, if information regarding surgery, chemotherapy, radiation therapy, or immunotherapy was absent, if treatment was limited to chemotherapy or RT alone, or if the RT dose fell outside the 57–74 Gy range. Situations where chemotherapy and RT were initiated non-concurrently, meaning separated by more than 30 days, also led to exclusion [29]. The total study sample was split into two distinct cohorts. Those diagnosed from 2004 through 2016 constituted the pre-immunotherapy-era group, while those diagnosed between 2017 and 2020 constituted the immunotherapy-era group. Any patient from the 2004–2015 window who had received immunotherapy was removed from the earlier cohort. In the immunotherapy group, immunotherapy was administered universally. We further excluded patients whose immunotherapy started before RT concluded or was delayed beyond 180 days post-RT, as well as those whose chemotherapy followed immunotherapy or whose immunotherapy began more than 180 days after chemotherapy.

Outcome and covariates

OS served as the primary study endpoint. The NCDB captures OS but lacks data on PFS, local disease control, or treatment toxicity. The RT dose represented the central covariate. Other variables incorporated into the analysis covered age at diagnosis (years), insurance coverage (yes or no), race and ethnicity, Charlson-Deyo Comorbidity Index scoring (0, 1, ≥ 2), facility type (academic/research versus non-academic), year of diagnosis, neighborhood educational attainment, T classification, N classification, group stage, and median household income. Neighborhood educational attainment in the NCDB is assigned by linking the patient's zip code at diagnosis to American Community Survey 2016 data and sorting into quartiles based on the percentage of residents aged ≥ 25 lacking a high school diploma (≥ 17.6%, 10.9–17.5%, 6.3–10.8%, and < 6.3%), which we subsequently dichotomized (< 10.9% for higher educational level and ≥ 10.9% for lower educational level). Median household income in the NCDB is determined through a parallel zip-code linkage to the American Community Survey 2016 and grouped into quartiles (< $40,227, $40,227–$50,353, $50,354–$63,332, and ≥ $63,333), which we collapsed into a binary variable (≥ $50,353 or < $50,353). Regarding immunotherapy sequencing with RT, three categories were created: initiation within 6 weeks of completing RT, at 7–10 weeks post-RT, and after 10 weeks post-RT. Immunotherapy sequencing with chemotherapy was similarly classified into three groups: start within ten weeks, between 11 and 14 weeks, and beyond 14 weeks from the start of chemotherapy. Assuming chemotherapy during the dcCRT component typically lasts about six weeks, these chemotherapy-to-immunotherapy intervals map to RT-completion-to-immunotherapy gaps of ≤ 4 weeks, 5–8 weeks, and > 8 weeks, respectively.

Statistical analysis

Descriptive summaries by race and ethnicity were presented as means with standard deviations (SD) for continuous measures and as counts with percentages for categorical measures. Multivariable logistic regression modeling generated odds ratios (ORs) and 95% confidence intervals (CIs) to identify factors independently associated with receipt of an escalated RT dose (64–74 Gy).

The Kaplan-Meier method was used to estimate median survival, and the log-rank test was used to assess differences in survival across RT dose strata. Cox proportional hazards regression modeling yielded hazard ratios (HRs) with 95% CIs for the effect of dose escalation on all-cause mortality among unresectable stage III NSCLC patients in both the pre-immunotherapy period (2004-2016) and the immunotherapy period (2017-2020). Survival duration was measured in months, from the date of diagnosis until death or the last documented follow-up. Individuals still alive at their last follow-up or lost to follow-up were treated as censored observations. The full suite of statistical analyses was executed with SAS version 9.4 (SAS Institute, Cary, NC).

Results and Discussion

The pre-immunotherapy cohort comprised 47,315 patients, while the immunotherapy cohort comprised 4,749 patients. These groups were assembled by applying the selection algorithm to patients treated with concurrent DC CRT followed by immunotherapy, restricting to stage III only, discarding surgical cases, and removing those with RT doses under 56 Gy or over 80 Gy. Demographic profiles for both cohorts are displayed in **Table 1**. Across both groups, a preponderance of subjects were male, white, diagnosed with squamous cell carcinoma, managed in community hospital settings, and carried a comorbidity score of zero. Those whose RT dose was in the 57–63 Gy range were more likely to live in neighborhoods with higher median incomes and higher educational attainment than recipients of an intermediate escalated RT dose (64–74 Gy). The 57–63 Gy group also had a higher probability of receiving treatment at academic facilities than the 64–74 Gy group. Individuals with more advanced N classification or group stage were more apt to be treated with the lower 57–63 Gy dose range. The absence of stage IIIC designations in the pre-immunotherapy era (2004-2016) reflects the shift from the 7th edition of the AJCC NSCLC staging framework to the 8th edition, implemented in 2017.

Table 1. Baseline characteristics of patients diagnosed with inoperable stage III NSCLC between 2004 and 2020 by RT dose for the era before immunotherapy and the era after its approval.

		The era of immunotherapy (2017-2020)				**Before the era of immunotherapy (2004-2016)**			
Variable		**Dose 57-63 Gy (n = 3,210, 67.6%)**	**P**	**Total (n = 4749)**	**Dose 64-74 Gy (n = 1,539, 32.4%)**	**Dose 57-63 Gy (n = 23,324, 49.3%)**	**P**	**Total (n = 47315)**	**Dose 64-74 Gy (n = 23,991, 50.7%)**
Age at diagnosis	Continuous (median and ranges)	67 (29-90)	0.22	67 (21-90)	66 (21-90)	65 (19-90)	0.001	67 (21-90)	65 (23-90)
Sex	Male	1,744 (54.3)	0.02	2,634 (55.5)	890 (57.8)	1,3308 (57.1)	0.001	27,476 (58.1)	14,168 (59.1)
	Female	1,466 (45.7)		2,115 (44.5)	649 (42.2)	10,016 (42.9)		19,839 (41.9)	9,823 (40.9)
Race	White	2,690 (84.2)	0.12	3976 (84.1)	1,286 (83.8)	19,679 (84.9)	0.001	39,942 (84.9)	20,263 (84.8)
	Black	387 (12.1)		593 (12.5)	206 (13.2)	2,859 (12.3)		5,950 (12.5)	3091 (13.0)
	Non-White non-Black	118 (3.7)		160 (3.4)	44 (3.0)	644 (2.8)		1,175 (2.5)	531 (2.2)
Histology	Adenocarcinoma	1,446 (45.0)	0.98	2,149 (45.2)	703 (45.7)	8,134 (34.9)	0.001	16,043 (33.9)	7,909 (33.0)
	Squamous cell carcinoma	1,638 (51.0)		2,415 (50.8)	777 (50.5)	9,950 (42.7)		20,427 (43.2)	10,477 (43.7)
	Large cell carcinoma	31 (1.0)		45 (1.0)	14 (0.9)	614 (2.6)		1,332 (2.8)	718 (3.0)
	Undifferentiated	95 (3.0)		140 (3.0)	45 (2.9)	4,626 (19.8)		9,513 (20.1)	4,887 (20.3)
Charlson/Deyo comorbidity score	0	1,841 (57.4)	0.14	2,708 (57.0)	867 (56.3)	14,402 (61.7)	0.01	29,249 (61.8)	14,847 (61.9)
	1	823 (25.6)		1,198 (25.2)	375 (24.4)	6,122 (26.3)		12,577 (26.6)	6,455 (26.9)
	≥ 2	546 (17.0)		843 (17.8)	297 (19.3)	2,800 (12.0)		5,489 (11.6)	2,689 (11.2)

Neighborhood education level	≥ 10.9% NHD	1,333 (49.3)	0.001	2,089 (52.2)	746 (58.3)	10,448 (50.1)	0.001	22,218 (52.4)	11,770 (54.6)
	< 10.9% NHD	1,372 (50.7)		1,913 (47.8)	541 (41.7)	10,416 (49.9)		20,184 (47.6)	9,768 (45.4)
Household income	< $50,353	1,251 (46.3)	0.001	1,957 (49.0)	706 (54.4)	9,691 (46.6)	0.001	21,007 (49.7)	11,316 (52.7)
	≥ $50,353	1,449 (53.7)		2,040 (51.0)	591 (45.6)	11,114 (53.4)		21,284 (50.3)	10,170 (47.3)
Treatment facility type	Academic	895 (28.0)	0.003	1,259 (26.6)	364 (23.8)	6,423 (27.7)	0.001	12,315 (26.2)	5,893 (24.7)
	Community	2,305 (72.0)		3,472 (73.4)	1,165 (76.2)	16,778 (72.3)		34,731 (73.8)	17,953 (75.3)
T stage	T1	574 (18.1)	0.45	833 (17.7)	259 (17.0)	3255 (15.0)	0.31	6,471 (14.8)	3216 (14.5)
	T2	733 (23.1)		1063 (22.6)	330 (21.7)	6848 (31.6)		13,865 (31.6)	7017 (31.6)
	T3	759 (23.9)		1135 (24.2)	376 (24.7)	4826 (22.3)		9,762 (22.3)	4936 (22.2)
	T4	1109 (34.9)		1666 (35.5)	557 (36.6)	6724 (31.1)		13,757 (31.4)	7033 (31.7)
N stage	N0	305 (9.6)	0.001	488 (10.4)	183 (12.0)	1692 (7.8)	0.001	3,800 (8.7)	2108 (9.5)
	N1	250 (7.9)		396 (8.4)	146 (9.6)	1281 (5.9)		2,774 (6.3)	1493 (6.7)
	N2	1891 (59.6)		2834 (60.3)	943 (62.0)	13324 (61.5)		27,745 (63.3)	14421 (65.0)
	N3	729 (23.0)		979 (20.8)	250 (16.4)	5356 (24.7)		9,536 (21.7)	4180 (18.8)
Group stage	IIIA	1548 (48.8)	0.001	2370 (50.5)	822 (54.0)	12,022 (55.5)		25,242 (57.6)	13,220 (59.5)
	IIIB	1335 (42.1)		1941 (41.3)	606 (39.8)	9,631 (44.5)		18,613 (42.4)	8,982 (40.5)
	IIIC	292 (9.2)		386 (8.2)	94 (6.2)	Not defined in AJCC 7th Edition			
Immunotherapy sequence with RT	Within 42 days of RT completion	1,857 (57.9)	0.2	2,759 (58.0)	902 (58.6)		0.001		
	43-70 days of RT completion	922 (28.7)		1,331 (33.8)	409 (26.6)				
	> 70 days of RT completion	431 (13.4)		659 (13.9)	228 (14.8)				
Immunotherapy sequence with chemo	Within 70 days after the start of chemotherapy	778 (24.2)	0.001	1,061 (13.6)	283 (18.4)				
	71-98 days after the start of chemotherapy	1507 (47.0)		2,211 (50.0)	704 (35.9)				

> 98 days after the start of chemotherapy	925 (28.8)	1,477 (36.4)	552 (41.9)

Abbreviation: NHD = no high school degree. P-values: calculated for comparisons between cohorts of IDE (64-74Gy) and SD (57-63Gy) for each demographic category.

Table 2. Percentage of patients by stage and immunotherapy sequence for the era after immunotherapy approval.

Immunotherapy sequence with RT	**Group stage**		
	IIIC	**IIIB**	**IIIA**
Within 42 days of RT completion	242 (62.7%)	1128 (58.1%)	1361 (57.4%)
43–70 days of RT completion	98 (25.4%)	556 (28.7%)	660 (27.9%)
> 70 days of RT completion	46 (11.9%)	257 (13.2%)	349 (14.7%)
Group stage	> 70 days of RT completion	43–70 days of RT completion	Within 42 days of RT completion
IIIA	349 (53.5%)	660 (50.2%)	1361 (49.8%)
IIIB	257 (39.4%)	556 (42.3%)	1128 (41.3%)
IIIC	46 (7.1%)	98 (7.5%)	242 (8.9%)

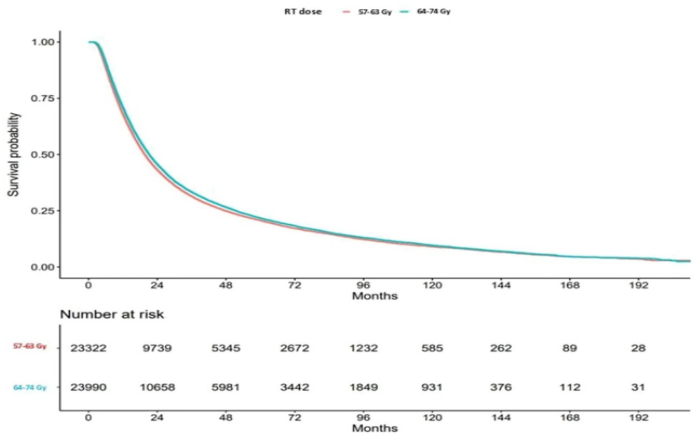
All percentages were calculated based on the total for each column.

A numerically greater proportion of patients with more advanced disease stages commenced immunotherapy closer to RT completion **(Table 2)**. To illustrate, 8.9% of stage IIIC patients initiated treatment within 6 weeks, compared with 7.1% who began more than 10 weeks after RT, while 49.8% of stage IIIA patients fell into the within-6-weeks window, compared with 53.5% who started beyond 10 weeks after RT.

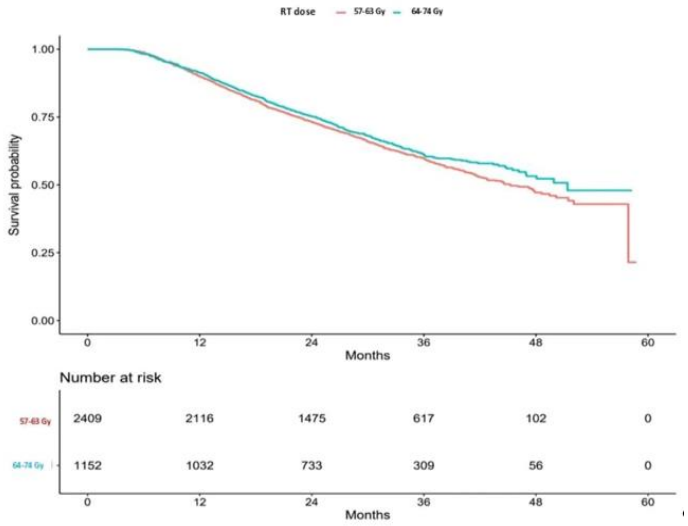
Survival outcomes

Before the era of immunotherapy

Within the pre-immunotherapy cohort—stage III NSCLC patients whose diagnoses fell between 2004 and 2016 and whose management consisted solely of definitive concurrent chemoradiation—the median follow-up duration was 71 months, and half the cohort survived at least 20.4 (95% CI: 20.2-20.7) months. A gap in median survival favoring the escalated arm was evident when outcomes were examined by RT dose band: 19.7 (95% CI: 19.3-20.0) months for 57–63 Gy versus 21.2 (95% CI: 20.8-21.5) months for 64–74 Gy ($P < 0.0001$) **(Figure 1a).** After building a multivariable Cox model that included terms for age at diagnosis, sex, race, income, education, facility type, comorbidity score, and histology, treatment in the 57–63 Gy stratum remained independently predictive of higher all-cause mortality relative to IDE spanning 64–74 Gy (HR: 1.09, 95% CI: 1.07-1.12; $P < 0.001$) **(Table 3)**.



a)



b)

Figure 1. Overall survival of patients with intermediate dose escalation (64-74Gy) vs. standard RT dose (57-63Gy); in the era of pre-immunotherapy (a), and for those who received adjuvant immunotherapy after dcCRT (b). Red curves: 57–63 Gy; blue curves: 64–74 Gy.

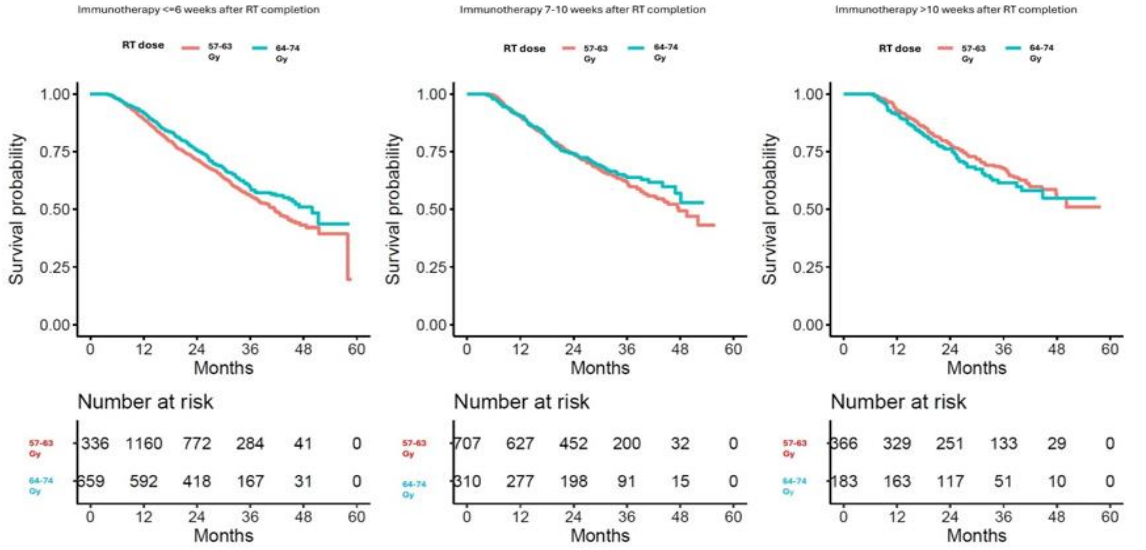
Table 3. Multivariable analysis of RT dose for all-cause mortality among 47,315 patients diagnosed with inoperable stage III NSCLC between 2004 and 2016 (pre-immunotherapy era).

Variable		P	Multivariable analysis
			HR (95% CI)
Age at diagnosis	Continuous (median and ranges)	0.001	1.01 (1.01-1.01)
RT dose	57–63 Gy	0.001	1.09 (1.07-1.12)
	64–74 Gy		Ref
Sex	Male	0.001	Ref
	Female		0.83 (0.82-0.85)
Race	White	0.001	Ref
	Black		0.91 (0.88-0.94)
	Non-White non-Black	0.001	0.82 (0.76-0.88)
Histology	Adenocarcinoma		Ref
	Squamous cell carcinoma	0.001	1.12 (1.09-1.15)
	Large cell carcinoma	0.001	1.13 (1.06-1.20)
	Other undifferentiated	0.001	1.11 (1.07-1.14)
Charlson/Deyo comorbidity score	0	0.001	Ref
	1		1.08 (1.05-1.10)
	≥ 2	0.001	1.16 (1.12-1.20)
Neighborhood education level	≥ 10.9% NHD	0.03	Ref
	< 10.9% NHD		0.97 (0.95-0.99)
Household income	< $50,353	0.001	Ref
	≥ $50,353		0.93 (0.91-0.96)
Treatment facility type	Academic	0.001	0.91 (0.89-0.93)
	Community		Ref

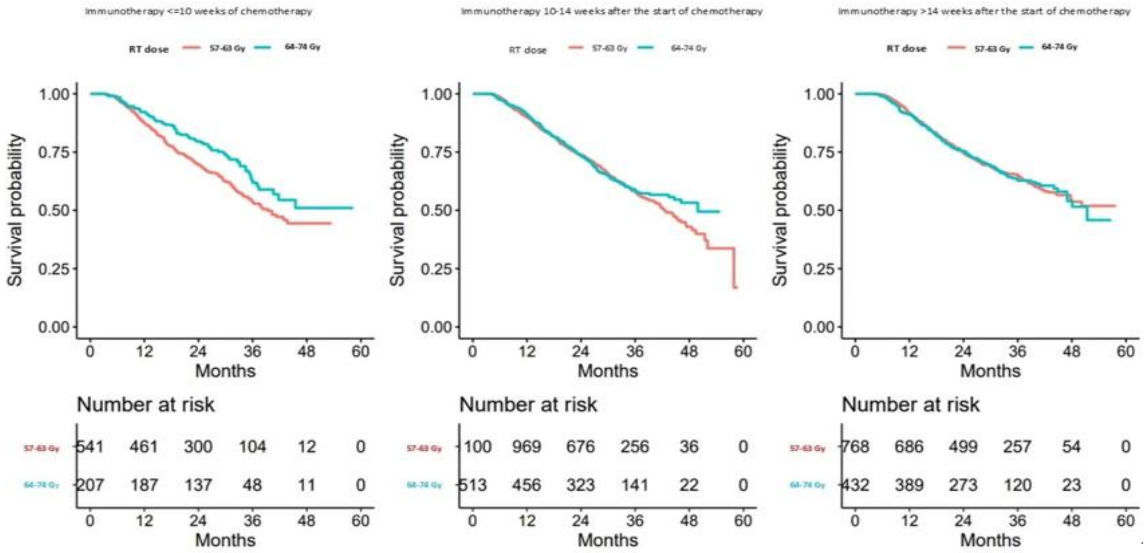
Era of immunotherapy

For the later cohort—stage III NSCLC diagnosed between 2017 and 2020, treated with definitive concurrent chemoradiation followed by adjuvant immunotherapy—median follow-up was 31 months, and median survival was estimated at 47.7 months (95% CI: 44.7-51.4). By dose level, median survival came to 45.2 (95% CI: 42.2-49.5) months in the 57–63 Gy group and 51.4 (95% CI: 46.9-not reached) months in the 64–74 Gy group (P = 0.0881) **(Figure 1b).**

When the analysis was conditioned on the time between completing RT and starting immunotherapy, the following patterns emerged. Where immunotherapy began within six weeks, median OS stood at 41.5 (95% CI: 38.0-44.6) months for 57–63 Gy versus 49.9 (95% CI: 43.4-not reached) months for 64–74 Gy (P = 0.03). Where initiation fell in the 6–10 week post-RT window, the 57–63 Gy arm had a median OS of 47.7 (95% CI: 42.7-not reached) months, and the 64–74 Gy arm had not reached (95% CI: 46.9-not reached) (P = 0.38). Where immunotherapy was delayed beyond ten weeks after RT, neither group reached its median OS: not reached (95% CI: 47.8-not reached) for 57–63 Gy and not reached (95% CI: 40.0-not reached) for 64–74 Gy (P = 0.40) **(Figure 2a)**. Taken together, these data suggest a graded improvement in OS with later immunotherapy initiation, a pattern evident in both dose strata. It is instructive that even the IDE patients who received immunotherapy within 6 weeks did not outperform standard-dose patients who deferred immunotherapy for at least 6 weeks after RT (HR: 0.96, 95% CI: 0.80-1.14; P = 0.66). The survival differential favoring IDE in the early-start subgroup was driven disproportionately by those who began immunotherapy within two weeks of RT completion (HR: 2.19, 95% CI: 1.32-3.62, P = 0.002 standard dose vs. IDE), with two-year survival rates of 65% (95% CI: 57%-73%) and 84% (95% CI: 76%-92%) for the standard and escalated arms, respectively.



a)



b)

Figure 2. Overall survival of patients with intermediate-dose escalation (64-74Gy) vs. standard RT dose (57-63Gy), stratified by the time of immunotherapy after completion of RT (a) or after the start of chemotherapy (b). Red curves: 57–63 Gy; blue curves: 64–74 Gy.

Reframing the analysis around the interval from chemotherapy initiation to immunotherapy start—using 10 weeks as the threshold, approximating 1 month after dcCRT—yielded complementary findings. Immunotherapy commencing within ten weeks of chemotherapy was associated with a median OS of 39.4 (95% CI: 35.1-not reached) months for 57–63 Gy and not reached (95% CI: 37.4-not reached) for 64–74 Gy (P = 0.01). In the 10–14 week window, median OS reached 42.7 (95% CI: 40.3-46.1) months for the 57–63 Gy arm and 49.9 (95% CI: 44.7-not reached) months for the 64–74 Gy arm (P = 0.43). For those starting beyond 14 weeks, median OS was not reached in either arm: not reached (95% CI: 47.7-not reached) for 57–63 Gy and 51.4 (95% CI: 46.9-not reached) for 64–74 Gy (P = 0.93) **(Figure 2b).**

Moving to multivariable (MVA) Cox regression, receipt of 57–63 Gy rather than 64–74 Gy was independently associated with excess all-cause mortality (HR: 1.17, 95% CI: 1.03-1.34; P = 0.02) **(Table 4).** Variables independently predicting lower mortality included female sex, African American race, a comorbidity score of at least 2, adenocarcinoma histology, and an interval exceeding 70 days between RT completion and immunotherapy **(Table 4).** Group stage—as opposed to the component T and N designations—trended toward a significant link with all-cause mortality/OS, consistent with expectation. Separate MVA Cox regressions comparing SD (57–63 Gy) with IDE (64–74 Gy) were then fitted within the pre-immunotherapy and immunotherapy cohorts, each stratified by T, N, and group stage **(Table 5)**. For the pre-immunotherapy period, SD consistently predicted a roughly 10% elevation in mortality risk across all T stages, higher N stages, and all group stages relative to IDE. The immunotherapy cohort, however, told a different story: the IDE advantage dissipated, with HR point estimates for SD no longer reaching significance in any T or N category. Strikingly, in the immunotherapy era, the SD arm demonstrated a significantly reduced hazard relative to IDE (HR: 0.86, 95% CI: 0.66-0.99, P = 0.047) **(Table 5).**

Table 4. Multivariable analysis of RT dose for all-cause mortality among 4,749 patients diagnosed with inoperable stage III NSCLC between 2017 and 2020 (immunotherapy era).

Variable		P	Multivariable analysis
			HR (95% CI)
Age at diagnosis	Continuous (median and ranges)	0.04	1.01 (1.00-1.02)
RT dose	57-63 Gy	0.02	1.17 (1.03-1.33)
	64-74 Gy		Ref
Immunotherapy sequence with RT	Within 42 days of RT completion		Ref
	43-70 days of RT completion	0.17	0.91 (0.79, 1.04)
	>70 days of RT completion	0.02	0.82 (0.69-0.99)
Sex	Male	0.001	Ref
	Female		0.78 (0.69-0.89)
Race	White		Ref
	Black	0.001	0.61 (0.49-0.76)
	Non-White non-Black	0.60	0.91 (0.64-1.29)
Histology	Adenocarcinoma		Ref
	Squamous cell carcinoma	0.001	1.44 (1.26-1.64)
	Large cell carcinoma	0.02	1.93 (1.11-3.37)
	Other undifferentiated	0.52	1.12 (0.79-1.60)
Charlson/Deyo comorbidity score	0		Ref
	1	0.03	1.17 (1.01-1.34)
	≥2	0.02	1.21 (1.03-1.42)
Neighborhood education level	≥10.9% NHD	0.07	Ref
	<10.9% NHD		1.15 (0.99-1.32)
Household income	<$50,353	0.04	Ref
	≥$50,353		0.86 (0.74-0.99)
Treatment facility type	Academic	0.77	1.02 (0.89-1.17)
	Community		Ref

T stage	T1		Reference
	T2	0.07	1.21 (0.99- 1.49)
	T3	0.17	1.20 (0.92-1.57)
	T4	0.30	1.17 (0.87-1.57)
N stage	N0		Reference
	N1	0.09	0.77 (0.57-1.04)
	N2	0.94	0.99 (0.72-1.35)
	N3	0.76	0.93 (0.56-1.53)
Group stage	IIIA		Reference
	IIIB	0.05	1.28 (1.00-1.64)
	IIIC	0.15	1.44 (0.88-2.36)

Table 5. MVA Cox regression for the OS of patients stratified by T, N, and group stage comparing standard dose (57–63 Gy) with IDE (64–74 Gy).

T stage	Era of immunotherapy	P	Before the era of immunotherapy	P
	HR (95% CI)		HR (95% CI)	
T1	1.24 (0.86-1.80)	0.25	1.09(1.02-1.15)	0.006
T2	1.08 (0.82-1.43)	0.60	1.09 (1.05-1.13)	0.001
T3	1.17 (0.89-1.54)	0.27	1.06 (1.01-1.11)	0.02
T4	1.15 (0.91-1.44)	0.24	1.11(1.07-1.15)	0.001
N stage				
N0	0.90 (0.60-1.35)	0.60	1.05 (0.97-1.13)	0.25
N1	1.17 (0.71-1.92)	0.55	1.07 (0.98-1.17)	0.13
N2	1.15 (0.97-1.36)	0.10	1.10 (1.07-1.13)	0.001
N3	1.31 (0.88-1.96)	0.18	1.07 (1.02-1.12)	0.008
Group stage				
IIIA	1.04 (0.86-1.25)	0.69	1.09 (1.06-1.12)	0.001
IIIB	0.81 (0.66-0.99)	0.047	1.09 (1.05-1.12)	0.001
IIIC	1.37 (0.83-2.28)	0.22	Not defined in AJCC 7th Edition	n/a

A key finding from the interval-stratified analysis was that the survival advantage attributable to IDE was confined exclusively to patients whose immunotherapy started within six weeks of RT completion (HR: 1.27, 95% CI: 1.08-1.51; P = 0.01), a cut-off that mirrors the PACIFIC trial design **(Table 6)**. The clinical relevance of this observation is underscored by the complete absence of a mortality difference between SD and IDE among those initiating immunotherapy at 7–10 weeks post-RT (HR: 1.13, 95% CI: 0.88-1.45; P = 0.35) or among those whose start fell beyond ten weeks (HR: 0.74, 95% CI: 0.51-1.07; P = 0.11) **(Table 6).**

Table 6. Hazard ratio and its 95% CI of RT dose for all-cause mortality stratified by immunotherapy time after RT completion.

Variable	P	HR 95% CI	Categories
Immunotherapy within 6 weeks of RT completion (42 days)			
RT dose	0.01	1.26 (1.05-1.6)	57–63 Gy
		Ref	64–74 Gy
Immunotherapy between 7–10 weeks (43–70 days) after RT completion			
RT dose	0.35	1.13 (0.88-1.45)	57–63 Gy

		Ref	64–74 Gy
Immunotherapy > 10 weeks (70 days) after RT completion			
RT dose	0.11	0.74 (0.51-1.07)	57–63 Gy
		Ref	64–74 Gy

The multivariable analysis was adjusted for age at diagnosis, gender, race, income, education, histology, comorbidity score, treatment facility type, T stage, N stage, and group stage.

A parallel picture was seen when the sequence was indexed to chemotherapy. Among patients whose immunotherapy started within ten weeks of the first chemotherapy dose, a 57–63 Gy RT dose was tied to worse all-cause mortality versus IDE (HR: 1.43, 95% CI: 1.06-1.92; P = 0.02) **(Table 7).** That excess risk vanished in the 10–14 week interval (HR: 1.19, 95% CI: 0.98-1.44; P = 0.08) and was absent when more than 14 weeks separated chemotherapy initiation from immunotherapy initiation (HR: 0.98, 95% CI: 0.78-1.24; P = 0.88) **(Table 7)**.

Table 7. Hazard ratio and its 95% CI of RT dose for all-cause mortality stratified by immunotherapy time after the start of chemotherapy.

Variable	P	HR 95% CI	Categories
Immunotherapy within 10 weeks of starting chemotherapy (42 days)			
RT dose	0.02	1.43 (1.06-1.92)	57–63 Gy
		Ref	64–74 Gy
Immunotherapy between 11–14 weeks (71–98 days) after the start of chemotherapy			
RT dose	0.08	1.19 (0.98-1.44)	57–63 Gy
		Ref	64–74 Gy
Immunotherapy > 14 weeks (98 days) after the start of chemotherapy			
RT dose	0.88	0.98 (0.78-1.24)	57–63 Gy
		Ref	64–74 Gy

The multivariable analysis was adjusted for age at diagnosis, gender, race, income, education, histology, comorbidity score, and treatment facility type.

What our study contributes is the most extensive retrospective evaluation yet assembled of whether IDE influences OS in unresectable stage III NSCLC managed with definitive chemoradiation, covering practice both before and, most consequentially, after immunotherapy's regulatory approval. The comparison we deliberately foregrounded was standard RT dosing of 60 Gy ± 10% vs. IDE (64–74 Gy); RT doses exceeding 74 Gy have been widely discarded since the RTOG 0617 findings were published. The NCDB data bear this out—after 2015, only 160 individuals (0.6%) were treated above the 74 Gy threshold. Our results indicate that among patients receiving dcCRT alone during the pre-immunotherapy period, shifting the RT dose to 64–74 Gy was associated with longer OS than maintaining a dose of 57–63 Gy. Yet the absolute gain—19.7 months versus 21.2 months, a separation of under 1.5 months—though statistically significant, is difficult to regard as clinically meaningful. This observation only strengthens the case for retaining 60 Gy as the benchmark definitive RT dose for stage III NSCLC in treatment eras before immunotherapy entered routine use.

Where our attention was most keenly directed, however, was the demonstration that, once immunotherapy became available, the survival increment attributable to intermediate RT dose escalation materialized exclusively when immunotherapy was initiated no later than six weeks after the final RT fraction. If immunotherapy was deferred into the 7–10 week window, or held beyond ten weeks post-RT, no mortality signal distinguished the 57–63 Gy and 64–74 Gy dose assignments. The broader pattern that emerged—a progressively widening gap between RT conclusion and immunotherapy initiation, paralleling improvements in OS—effectively removes the rationale for dose escalation. The same finding held when we shifted the reference point to chemotherapy start rather than RT end. Since the NCDB does not capture the date chemotherapy concludes, we used the interval from chemotherapy initiation to immunotherapy initiation as an additional treatment-sequencing surrogate, reasoning that, with

chemotherapy nearly always begun alongside RT, a ten-week landmark from the first chemotherapy dose approximates one month after chemotherapy finishes. Once again, IDE's benefit was detectable only when immunotherapy followed the start of chemotherapy—and thus, by extension, the completion of chemoradiation—at briefer intervals.

To contextualize these observations and explore their underpinnings, it is worth reflecting on the principal clinical variables that likely shape a treating physician's choice regarding when to commence immunotherapy after dcCRT. Based on our own clinical experience, these decisions typically revolve around the extent of disease at initial diagnosis and the tumor's response to dcCRT, the trajectory—whether accelerated or protracted—of patient recovery or residual functional compromise from dcCRT toxicities, and/or disparities in healthcare access. The last of these is plainly at odds with our data.

One way to read our findings would be to suppose that individuals who both started immunotherapy within six weeks and received IDE were simply in better overall condition—possessing, for instance, a performance status that permitted safe delivery of a higher radiation dose—compared with those given 57–63 Gy on a similarly compressed immunotherapy timeline. Arguing against this interpretation is the fact that the proportions of patients carrying comorbidity scores of zero, one, and two were broadly comparable between these two arms **(Table 1).** We fully grant that comorbidity indices do not equate to performance status, but NCDB's incomplete performance status fields left us with no alternative but to use comorbidity as a proxy. A related suggestion might be that patients who proceeded to immunotherapy within six weeks had less advanced disease at diagnosis and/or bounced back more quickly from dcCRT. What our data show, however, runs counter to that expectation: a numerically larger fraction of patients with higher-stage disease—stage IIIC, for example—were in the ≤6-week immunotherapy start group rather than the later-start groups **(Table 2)**, and these same higher-stage individuals were more likely to have been treated with the lower RT dose **(Table 1)**. This configuration is entirely compatible with a clinical logic wherein physicians, mindful of RT toxicity risks in the setting of bulkier disease or larger treatment fields, select a standard dose, yet simultaneously feel compelled to begin immunotherapy sooner out of concern for tumor progression in advanced-stage cancer, irrespective of whether the patient has adequately recovered from dcCRT—a sequence of decisions that could amplify harm. Our MVA further intimates that IDE may not merely lack OS benefit but could actually impair OS among those with more advanced NSCLC **(Table 5)**. We would propose, then, that the OS advantage associated with IDE in the ≤6-week immunotherapy subgroup is largely carried by better outcomes among lower-stage patients who received IDE, juxtaposed against higher-stage patients who received SD—a subset disproportionately represented in the early-start cohort. It is important to stress that this interpretation does nothing to undermine the core message: that permitting a longer interval before starting immunotherapy, and doing so with standard-dose RT, can match or exceed the results of shortened-interval IDE while exposing patients to potentially fewer toxicities.

A different explanatory angle is that commencing immunotherapy immediately or very shortly after dcCRT runs the risk of systematically excluding from the denominator those patients who develop rapid disease progression while receiving, or soon after finishing, dcCRT. In this scenario, IDE might have suppressed some of these early failures, thereby creating an apparent OS advantage. Such rapid-progression cases are not hypothetical; they occur in everyday practice and were documented in the PACIFIC experience, although their occurrence within the first month or two after RT is genuinely uncommon, as the PFS curves from Patel *et al*. [30] make clear. Moreover, their frequency has dwindled further in current practice, given that restaging body CT imaging is standard before immunotherapy initiation. Another telling detail is that deeper analysis localized IDE's survival advantage entirely to the subset starting immunotherapy within two weeks of RT completion (HR: 2.19, 95% CI: 1.32-3.62, P = 0.002 standard dose vs. IDE), accompanied by two-year survival rates of 65% (95% CI: 57%-73%) and 84% (95% CI: 76%-92%) for standard and escalated dosing, respectively. It is difficult to credit the second hypothesis when such a tiny window of unobserved potential disease progression would need to account for an overall survival difference of more than 5 percentage points.

A third explanatory model holds that dcCRT leaves a measurable imprint on immune function and that a recuperative interval must elapse before immunotherapy can operate at full potency. The mechanisms could involve depletion of tumor-infiltrating lymphocytes—indispensable cellular effectors of anti-tumor immunity—by conventionally fractionated RT, and/or the mobilization of myeloid-derived suppressor cells alongside tumor-associated macrophages, cell populations that promote neovascularization and tumor regrowth [31, 32]. The premise here is that the earliest cycles of immunotherapy, if administered too soon—within 2 weeks or up to 6 weeks after RT completion—contribute little to nothing, thereby eroding the survival gains immunotherapy would

otherwise deliver. This concept is buttressed by clinical observations cautioning against overly rapid sequencing of immunotherapy after conventionally fractionated RT [33-36]. Only under such conditions, we argue, would the benefit of IDE surface—a benefit that the full immunotherapy effect, when permitted sufficient delay, would normally render invisible. This model provides the best fit to our data: OS was consistently better when immunotherapy was postponed for at least 6 weeks beyond both RT and chemotherapy completion, regardless of whether the RT dose was standard or escalated. The OS advantage of IDE shrank as the interval to immunotherapy increased. If correct, the model suggests that although IDE coupled with immunotherapy within six weeks of RT was linked to better OS relative to 57–63 Gy, dose intensification becomes unnecessary once chemoradiation is followed by immunotherapy, provided the delay allows the host immune system to reconstitute fully. Further supporting evidence came from within-dose subgroup comparisons: among standard-dose (57–63 Gy) recipients, deferring immunotherapy beyond six weeks post-RT was associated with significantly better OS compared with starting at or before six weeks (HR: 0.83, 95% CI: 0.72-0.95; P = 0.01), whereas among IDE (64–74 Gy) recipients, no OS distinction could be drawn between early (≤ 6 weeks) and later (> 6 weeks) immunotherapy starts (HR: 0.98, 95% CI: 0.79-1.23; P = 0.88). These subgroup comparisons, taken together with the median OS estimates presented in the Results section, reinforce the conclusion that early immunotherapy initiation is deleterious when the RT dose is held at the standard level. IDE may partially offset the harm of starting immunotherapy prematurely, defined as within six weeks of RT.

This third hypothesis coheres with the immune-damage thesis articulated by Jin *et al*. [37], whose secondary analysis of RTOG 0617 established a correlation between higher RT doses—especially to the circulating immune cell pool—and shortened OS, underscoring that elevated RT doses exert a powerful depleting effect on immune cells and, once more, indicating that immunotherapy delivered in the immediate aftermath of RT may be the wrong strategy.

A point that warrants particular attention is the divergence between our findings—where delaying immunotherapy initiation rather than starting it early was associated with a trend toward better OS in both the standard-dose and IDE cohorts—and the directional signals reported from the PACIFIC and PACIFIC-R experiences. In those two analyses, shorter intervals appeared numerically linked to survival improvement, though post-hoc testing in neither study yielded statistical significance. An important methodological distinction is at play here: the PACIFIC trial measured survival time (OS or PFS) from randomization, a time point that occurred after the completion of dcCRT. Similarly, PACIFIC-R anchored all time-to-event calculations to the date durvalumab was first given, termed the PACIFIC-R index date. Neither investigation calculated survival from the date of cancer diagnosis, as we did in the present study. Because patients who started durvalumab sooner had their survival clock begin earlier—potentially by a matter of months—a lead-time bias could have been introduced in both the PACIFIC and PACIFIC-R designs, making PFS and OS appear artificially “longer” for early starters without necessarily reflecting a genuine extension of life when measured from diagnosis. This disparity in methodology further reinforces the argument that definitive resolution will require future prospective randomized clinical trial(s).

The body of evidence presented here collectively suggests that the timing of immunotherapy initiation after dcCRT, when appropriately selected, may improve OS. Yet the identity of the most predictive, clinically accessible factor—or set of factors—that defines the optimal starting point remains obscure. A significant line of investigation suggests that, within the tumor microenvironment (TME), the absolute counts of immune cells, including T cells specifically, matter less than the ratios between infiltrating immune subsets, such as CD8 to CD4 cells, which may better reflect the immunostimulatory properties of the tumor. Because of the difficulties inherent in obtaining repeated tumor tissue samples, a key unresolved question is whether systemic immune cell numbers and their subtype profiles following dcCRT can substitute for the cellular composition of the tumor microenvironment. However, the data suggest this may be the case [38]. The systemic immune-inflammatory index (SII), most often computed as a composite index combining platelet counts with peripheral blood neutrophil and lymphocyte measurements, has emerged as a prognostic marker in advanced-stage NSCLC [39, 40]. The challenge of how to link an individual patient’s SII to the immune cell landscape of their TME, and thereby pinpoint the ideal moment for immunotherapy delivery to optimize tumor control, remains unanswered and will probably necessitate, in upcoming clinical trials, more intensive serial sampling of immune cells drawn from both peripheral blood and tumor tissue.

What lends our study its strength is the sheer size of the sample, which provided enough statistical power to control for several meaningful confounders and to break the cohort down by the time separating RT completion from immunotherapy initiation—permitting the question of dose escalation to be examined with a level of detail

that a large dataset uniquely allows. Among the constraints are the retrospective design, the lack of information on local disease control, treatment-related toxicity, the concurrent chemotherapeutic agents used with radiation, the specific immunotherapy administered, and whether patients received one or more lines of immunotherapy. We are left to infer that, at minimum, the preponderance of patients in the immunotherapy-era cohort were treated with durvalumab in keeping with NCCN recommendations, since durvalumab stands alone as the agent granted FDA approval for adjuvant immunotherapy in unresectable stage III NSCLC following dcCRT, based on the phase III PACIFIC trial that demonstrated significant PFS and OS improvements over dcCRT alone. Further limiting our analysis is the absence of data detailing chemotherapy types, RT dosimetric parameters, and treatment planning techniques such as 3D conformal versus IMRT. It also bears acknowledging that we cannot determine whether a longer gap from the end of dcCRT to the start of immunotherapy reflected a more favorable or less favorable tumor response to the preceding chemoradiation. In everyday clinical practice, the tendency is to initiate immunotherapy within 42 days, following the PACIFIC trial template, regardless of the tumor's response to dcCRT. A complete clinical response to dcCRT, for instance, does not inherently dictate an earlier or later commencement of durvalumab infusion. More often than not, the interval in real-world settings is determined by how quickly follow-up CT body imaging can be coordinated after dcCRT, rather than by the treatment response itself. The significance of this question is considerable, yet an answer can only be supplied by a prospective randomized trial that stratifies patients according to their response to dcCRT.

Conclusion

Drawing on this extensive NCDB analysis, RT dose escalation to 64–74 Gy was not associated with better outcomes among stage III unresectable NSCLC patients whose immunotherapy began more than 6 weeks after chemoradiation. A greater separation between the end of RT and the start of immunotherapy is associated with improved OS. This relationship may remove the rationale for dose escalation altogether, since benefit was observed only in those who commenced immunotherapy within 6 weeks of completing RT. Our data reinforce that 60 Gy delivered in 30 fractions should remain the standard RT dose even in the immunotherapy era. Still, they also raise the question of whether a later launch of immunotherapy—specifically, beyond six weeks after dcCRT finishes—could confer an advantage. These results call for future prospective studies examining the marriage of immunotherapy and chemoradiation in the setting of intermediate RT dose escalation.

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Ethics Statement: The NCDB data is de-identified and does not require IRB approval. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from participants or their legal guardians/next of kin, in accordance with national legislation and institutional requirements. The NCDB data is de-identified and does not require informed consent.

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