Concurrent Chemoradiation With or Without Durvalumab in Elderly Patients With Unresectable Stage III NSCLC: Safety and Efficacy

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ABSTRACT

Introduction: The addition of durvalumab after chemoradiation therapy (CRT) in unresectable stage III NSCLC significantly improves survival. The benefit of this approach in elderly patients is controversial given the toxicity associated with CRT and, thus, may be underutilized. We sought...
to investigate the outcomes of elderly patients treated with CRT without or without durvalumab at our center.

**Methods:** We reviewed all stage III patients with NSCLC treated with CRT between 2018 and 2020. Patients were analyzed on the basis of age: less than 70 years and 70 years and older. The end points evaluated were treatment patterns, toxicity, progression-free survival, and overall survival.

**Results:** The baseline characteristics including Eastern Cooperative Oncology Group performance status and comorbidities were similar among the 115 patients (44 elderly, 71 young). Completion rates of CRT (100%, 97%) and chemotherapy dose intensity (97%, 97%) were high in elderly and young patients, respectively. There was a trend toward increased hospitalizations in elderly patients because of infections (27% versus 13%, \( p = 0.08 \)). Of those who did not have primary progression after CRT, 78% of elderly and 81% of young patients received durvalumab. The incidence of grade 3 or higher immune-related adverse events was 9% in elderly and 6% in young patients ( \( p = 0.67 \)). The median progression-free survival was similar (15.6 versus 10.5 mo, \( p = 0.10 \)), even after adjusting for comorbidities (hazard ratio = 0.6, \( p = 0.09 \)). The 12-month overall survival rates were 78% in the elderly and 76% in young patients ( \( p = 0.98 \)).

**Conclusions:** Well-selected elderly patients can be treated safely with CRT followed by durvalumab with similar survival benefits compared with their younger counterparts. We would advocate for the referral of all elderly patients for oncologic assessment to avoid undertreatment.

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**Keywords:** Elderly; Chemoradiotherapy; Immune checkpoint inhibitors; Multimodality treatment; Safety

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**Introduction**

The management of elderly patients with NSCLC is particularly challenging in locally advanced disease, in which the clinicians must balance toxicities from combined modality treatments with potentially curative therapy.\(^1,2\) Data from the PACIFIC study established the addition of year-long consolidative immunotherapy with durvalumab after definitive chemoradiation therapy (CRT) as the new standard of care for unresectable stage III NSCLC.\(^3,4\) There is a paucity of studies on this treatment approach in elderly patients and data on safety and outcomes are urgently needed to help inform treatment decisions.

Concern exists surrounding the use of CRT in elderly patients and the literature contains conflicting results.\(^5–9\) Stinchcombe et al.\(^5\) performed a pooled analysis with individual patient data on patients 70 years and older enrolled in 16 prospective cooperative group studies investigating CRT in stage III NSCLC, and found that elderly patients suffered worse overall survival (OS) and more toxicity than their younger counterparts. However, half of the included studies in this pooled analysis were performed more than 15 years ago and do not necessarily reflect the outcomes of patients treated with modern CRT and associated supportive measures.\(^5\) The relative safety of contemporary CRT is implied in the PACIFIC study, which enrolled 158 patients 70 years and older.\(^3,4,9\) Although a post hoc analysis in patients 70 years and older found tolerability of durvalumab, the toxicities of CRT were not captured because patients were randomized after completion of CRT.\(^9\)

Epidemiologic studies suggest that elderly patients with lung cancer may be undertreated.\(^10\) Firtal et al.\(^10\) identified age as an independent factor in patient selection for CRT in stage III NSCLC. In the era of consolidative immunotherapy, the decision to forego CRT can be detrimental to survival as it may preclude subsequent access to immunotherapy in the curative setting. We, therefore, sought to describe the tolerability and survival outcomes of CRT followed by durvalumab in the elderly compared with young patients in a large academic cancer center.

**Materials and Methods**

We conducted a review of all unresectable stage III patients with NSCLC treated with curative-intent CRT at the Princess Margaret Center Centre between 2018 and 2020. Comorbidities were standardized using the validated Charlson comorbidity index.\(^7\) The study end points were the following: (1) practice patterns, including the radiotherapy dose, chemotherapy regimens, and use of consolidation durvalumab; (2) toxicities to CRT and durvalumab; (3) overall response rates (ORRs); and (4) survival outcomes to treatment. All axial imaging was reviewed by the study investigator (SL) on the study team to determine the best response and date of progression according to the Response Evaluation Criteria in Solid Tumors version 1.1 and any uncertainties were reviewed by a senior investigator (AG). All study procedures were performed in accordance with the protocols approved by the University Health Network research ethics board. As the study was retrospective, informed consent was not required by the review board.

**Statistical Analysis**

Patients were analyzed according to age: younger than 70 years and 70 years and older. Patient
characteristics, practice patterns, and adverse events (AEs) were summarized descriptively and compared across age groups using Fisher’s exact tests for categorical variables and the Kruskal-Wallis test for continuous variables. The ORRs were determined according to the Response Evaluation Criteria in Solid Tumors version 1.1. The progression-free survival (PFS) and OS were calculated using the Kaplan-Meier method and tested for differences using the log-rank test. Multivariable Cox regressions were performed to adjust for confounding factors. Sensitivity analysis was performed among patients with EGFR/ALK wild-type NSCLC. All statistical analyses were performed using R version 4.0.2 (R Project for Statistical Computing; available at https://www.R-project.org/).

### Results

#### Patient Characteristics and Treatment Patterns

Between 2018 and 2020, there were 115 patients with unresectable stage III NSCLC treated with CRT: 44 elderly patients (ages 70–89 y) and 71 young patients (ages 34–69 y). Baseline characteristics, summarized in Table 1, were similar between elderly and young patients, including Eastern Cooperative Oncology Group performance status, comorbidities, and programmed death-ligand 1 expression levels.

With the exception of two patients who could not complete CRT owing to disease progression and treatment-related death, all patients received definitive radiotherapy doses of at least 60 Gy in 30 daily fractions. All patients were treated with intensity-modulated radiotherapy technique and daily image guidance using...

### Table 1. Patient Characteristics

| Baseline Characteristic | All Patients N = 115, n (%) | Elderly Patients n = 44, n (%) | Young Patients n = 71, n (%) | p Value |
|-------------------------|-----------------------------|-------------------------------|-------------------------------|---------|
| Age range              | 34-90                       | 70-90                         | 34-70                         | 0.33    |
| Sex                     |                             |                               |                               |         |
| Male                    | 66 (57)                     | 28 (64)                       | 38 (54)                       |         |
| Female                  | 49 (43)                     | 16 (36)                       | 33 (46)                       |         |
| Ethnicity               |                             |                               |                               | 1.0     |
| White                   | 84 (76)                     | 33 (77)                       | 51 (76)                       |         |
| Asian                   | 23 (21)                     | 9 (21)                        | 14 (21)                       |         |
| Other                   | 3 (3)                       | 1 (2)                         | 2 (3)                         |         |
| Smoking                 |                             |                               |                               | 0.12    |
| Nonsmoker               | 31 (27)                     | 10 (23)                       | 21 (30)                       |         |
| Exsmoker                | 62 (54)                     | 29 (66)                       | 33 (46)                       |         |
| Current smoker          | 22 (19)                     | 5 (11)                        | 17 (24)                       |         |
| ECOG                    |                             |                               |                               | 0.14    |
| 0                       | 38 (35)                     | 10 (24)                       | 28 (41)                       |         |
| 1                       | 69 (63)                     | 31 (74)                       | 38 (56)                       |         |
| ≥2                      | 3 (3)                       | 1 (2)                         | 2 (3)                         |         |
| Charlson comorbidity index median (range) | 1 (0-5) | 1 (0-4) | 0 (0-5) | 0.13 |
| Stage                   |                             |                               |                               | 1.0     |
| 3A                      | 69 (60)                     | 26 (59)                       | 43 (61)                       |         |
| 3B                      | 39 (34)                     | 15 (34)                       | 24 (34)                       |         |
| 3C                      | 7 (6)                       | 3 (7)                         | 4 (6)                         |         |
| Tumor histology         |                             |                               |                               | 0.096   |
| Adenocarcinoma          | 72 (63)                     | 22 (50)                       | 50 (70)                       |         |
| Squamous                | 35 (30)                     | 18 (41)                       | 17 (24)                       |         |
| Other                   | 8 (7)                       | 4 (9)                         | 4 (6)                         |         |
| PD-L1                   |                             |                               |                               | 0.57    |
| <1%                     | 37 (37)                     | 15 (41)                       | 22 (35)                       |         |
| 1%-49%                  | 31 (31)                     | 9 (24)                        | 22 (35)                       |         |
| >50%                    | 32 (32)                     | 13 (35)                       | 19 (30)                       |         |
| EGFR mutation           |                             |                               |                               | 0.56    |
| Present                 | 16 (21)                     | 4 (15)                        | 12 (24)                       |         |
| Absent                  | 61 (79)                     | 22 (85)                       | 39 (76)                       |         |
| ALK mutation            |                             |                               |                               | 0.26    |
| Present                 | 9 (11)                      | 1 (4)                         | 8 (15)                        |         |
| Absent                  | 71 (89)                     | 25 (96)                       | 46 (85)                       |         |
| Best response to chemoradiation |           |                               |                               | 0.39    |
| Complete/partial response | 49 (43)                   | 22 (51)                       | 27 (39)                       |         |
| Stable disease          | 52 (46)                     | 18 (42)                       | 34 (49)                       |         |
| Progressive disease     | 12 (11)                     | 3 (7)                         | 9 (13)                        |         |

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.
6% of young patients (3 or higher esophagitis was reported in 9% of elderly and AEs experienced by both age groups. The incidence of grade CRT-Related Toxicities

The use of granulocyte colony-stimulating factor in both groups was low (9% versus 3%, \( p = 0.2 \)). However, there was a trend to increased hospitalization rates in elderly patients (27% versus 13%, \( p = 0.08 \)), mostly attributed to febrile neutropenia and nonneutropenic infections. There were two treatment-related deaths because of neutropenic sepsis, one in each age group. Other treatment-related AEs are summarized in Table 3.

Immune-Related Toxicities

Durvalumab was well tolerated by both elderly and young patients. The rate of any immune-related AEs (irAEs) grade 3 or higher was 9% in the elderly and 6% in young patients (\( p = 0.67 \)). The details of irAEs are summarized in Table 3. Systemic steroids were required in 64% of elderly and 55% of young patients (\( p = 0.58 \)). The occurrence of irAE led to the permanent discontinuation of durvalumab in 50% of the elderly and 34% of young patients (\( p = 0.39 \)).

All-cause pneumonitis was the most common AE reported during treatment with durvalumab: 41% (3% grade ≥3) in elderly and 34% (6% grade ≥3) in young patients (\( p = 0.64 \)). There was a trend toward higher rates of immune-related pneumonitis, in which inflammatory changes clearly occurred outside the radiation field, in elderly patients (22% versus 8%, \( p = 0.099 \)). The median time from completion of CRT to the onset of all-cause pneumonitis and immune-related pneumonitis was 90 days and 99 days, respectively. The timing of pneumonitis was not statistically different between elderly and young patients. Durvalumab was rechallenged in 63% (\( n = 19 \)) of

cone-beam computed tomography as per current institutional policy. A platinum doublet, in combination with etoposide, pemetrexed, or paclitaxel, was used concurrently with radiotherapy. The use of carboplatin was more common in elderly patients (70% versus 46%). The dose intensity of chemotherapy and the number of planned cycles received were similar between elderly and young patients (Table 2).

After CRT, 78% (32 of 41) of elderly and 81% (50 of 62) of young patients who did not have primary progressive disease received durvalumab. The reasons for not receiving durvalumab were patient/clinician preference (67% versus 42%), toxicity from CRT (33% versus 8%), surgical resection after CRT (0% versus 33%), and contraindications to immunotherapy (0% versus 17%) in the 11 elderly and 12 young patients, respectively. The median time to starting durvalumab was similar between elderly and young patients (44 versus 36.5 d). At the time of analysis, 91% of elderly and 80% of young patients had stopped durvalumab, of which 31% and 25% were because of completion of consolidation therapy, respectively.

CRT-Related Toxicities

Eosophagitis and neutropenia were the most common AEs experienced by both age groups. The incidence of grade 3 or higher esophagitis was reported in 9% of elderly and 6% of young patients (\( p = 0.48 \)). Despite the more frequent use of carboplatin and the associated risk of myelosuppression in elderly patients, the incidence of grade 3 or higher neutropenia was similar (30% versus 37%, \( p = 0.54 \)).

### Table 2. CRT Treatment Patterns

| Regimen Details | All Patients N = 115, n (%) | Elderly Patients n = 44, n (%) | Young Patients n = 71, n (%) | \( p \) Value |
|-----------------|----------------------------|--------------------------------|----------------------------|-------------|
| **Chemotherapy** |                            |                                |                            |             |
| Platinum        |                            |                                |                            |             |
| Cisplatin       | 51 (44)                    | 13 (30)                        | 38 (54)                    | 0.013       |
| Carboplatin     | 64 (56)                    | 31 (70)                        | 33 (46)                    |             |
| **Regimens**    |                            |                                |                            | 0.67        |
| Platinum/etoposide\(^a\) | 66 (57)                    | 25 (57)                        | 41 (58)                    |             |
| Platinum/pemetrexed\(^b\) | 22 (19)                    | 7 (16)                         | 15 (21)                    |             |
| Carboplatin/paclitaxel\(^c\) | 27 (23)                    | 12 (27)                        | 15 (21)                    |             |
| **Chemotherapy dose intensity** | Mean (SD)                  |                                |                            | 0.83        |
| Percentage of planned chemotherapy cycles received | 96.9% (8.9)                 | 96.8% (9.6)                    | 97.0% (8.4)               |             |
| **Radiotherapy** |                                |                                |                            |             |
| Mean radiotherapy dose | 60 (18-85)\(^d\)            | 60 (58-70)\(^d\)              | 60 (18-85)\(^d\)          | 0.97        |

\(^a\)Combination of cisplatin 50 mg/m² on days 1 and 8 or carboplatin AUC 5 plus etoposide 50 mg/m² on days 1 to 5 every 21 to 28 days for two cycles.

\(^b\)Combination of cisplatin 75 mg/m² or carboplatin AUC 5 on day 1 plus pemetrexed 500 mg/m² on day 1 every 21 days for 2 to 3 cycles.

\(^c\)Combination of cisplatin AUC 2 on day 1 and paclitaxel 45 mg/m² on day 1 every week for 6 weeks.

\(^d\)Definitive RT dosing was delivered at 60 to 66 Gy. Significantly lower doses of RT (<58 Gy) in two patients were a result of primary disease progression or treatment-related death. Patients who received more than 66 Gy were enrolled in a clinical study of PET-directed adaptive radiation dose escalation.

AUC, area under the curve; CRT, chemoradiation therapy; PET, positron emission tomography; RT, radiation therapy.
patients with all-cause pneumonitis. Among the 19 patients rechallenged, 12 (63%) were successful with no recurrence of pneumonitis or other irAE, six (32%) experienced a different irAE and one (5%) developed a recurrence of pneumonitis. This included one patient with immune-related pneumonitis who was rechallenged successfully with durvalumab. Durvalumab was permanently discontinued in all other patients (n = 10) who experienced immune-related pneumonitis.

Immune-related endocrinopathies were common and reported in 28% of elderly and 18% of young patients. There were two cases of diabetic ketoacidosis, both of which occurred in elderly patients. Rates of immune-related colitis were low and not different between elderly and young patients (3% versus 12%). All other occurrences of uncommon irAEs are summarized in Table 3.

**Outcomes**

The average scan intervals for patients who had at least stable disease after CRT were 2.9 months (SD =
1.32) elderly and 2.6 (SD = 1.35) months in young patients (p = 0.09). There was a trend toward a longer PFS in the elderly patients, with median PFS from the start of CRT of 15.6 months versus 10.5 months, even after adjusting for comorbidities (hazard ratio = 0.6, p = 0.10) (Fig. 1A). The OS was also similar between the age groups, with 2-year survival rates of 77% in both groups (p = 0.98) (Fig. 1B).

In a subgroup analysis of EGFR and ALK wild-type patients, elderly patients had a longer median PFS (24.6 versus 10.5 mo, p = 0.06). The 2-year OS rates remain similar in the elderly and young EGFR and ALK wild-type patients (78% versus 76%, p = 0.51).

Elderly patients who received durvalumab exhibited a similar ORR compared with young patients (50% versus 45%, p = 0.81). The median PFS calculated from the start of durvalumab was 13.6 months for all patients and not different between the elderly and young (not reached versus 13.4 mo, p = 0.14) (Fig. 1C). At the time of progression, 24% of the elderly and 25% of the young died...
from their disease. Further cancer-directed therapies were given to 57% of elderly and 70% of young patients \((p = 0.4)\) and included curative-intent salvage therapy in two elderly and three young patients. The median OS has not been reached, the 24-month OS rates were 84% in the elderly and 70% in young patients \((p = 0.98)\). (Fig. 1D).

**Discussion**

To best of our knowledge, this is the first real-world study to report on elderly-specific outcomes in patients with unresectable stage III NSCLC treated with curative-intent CRT followed by durvalumab. Our results reveal that this treatment approach is safe and effective in older patients. More importantly, there is no significant increase in grade 3 or higher AEs in this selected elderly population, although a trend to a higher risk of infections requiring hospitalization necessitates close follow-up. The median PFS among elderly patients receiving durvalumab in our study, which is comparable to that reported in PACIFIC,\(^3,4\) underscores the effectiveness of consolidative immune checkpoint inhibitors in elderly patients.

Patients in our study, regardless of age, had high CRT completion rates with minimal treatment breaks and dose reductions, which speaks to the increasing safety of combined modality treatment over time. Two prospective elderly-specific CRT trials, Japan Clinical Oncology Group (JCOG9812) and JCOG0301, illustrate the importance of radiotherapy quality assurance.\(^11,12\) JCOG9812, which investigated the use of CRT with low-dose carboplatin, was closed early due to excess deaths which were partly attributed to deviations from the specified radiotherapy protocol.\(^11\) In a follow-up study (JCOG0301), which investigated the same regimen with strict quality control, superior survival of CRT over radiation therapy (RT) alone was observed in the elderly.\(^12\)

At our center, all patients receiving definitive CRT are reviewed at radiotherapy quality assurance rounds. Patients also receive weekly assessments during active treatment, allowing for early intervention with supportive measures, such as intravenous hydration, pain control, or oral antibiotics to avoid hospitalization. In addition, the radiotherapy techniques used in this study (intensity-modulated radiotherapy technique and image-guided RT) represent significant technical improvements over the field-based techniques used in the JCOG studies and are associated with improved clinical outcomes.\(^13\)

Contemporary population-based studies have similarly found that elderly patients benefit from curative-intent treatment.\(^6,14,15\) Miller et al.\(^6\) analyzed over 10,000 patients 70 years and older in the National Cancer Institute database with non-surgically-treated stage III NSCLC and reported superior OS among elderly patients treated with CRT compared with RT alone. In another single-institution study of 189 patients with stage III NSCLC, advanced age alone was not predictive of outcomes and elderly patients who received CRT had superior survival compared with RT alone.\(^15\) Combined with our findings that consolidation durvalumab after CRT was efficacious in the elderly and did not contribute significant additional toxicity, this suggests that an aggressive approach in older patients should be considered.

As we are only able to report on the outcomes of patients who were treated at our center, the impact of patient selection bias needs to be considered. It is likely that only select fit elderly patients are being referred for aggressive treatment. However, the potential for bias, in which only fit patients are treated, cannot be eliminated even in a prospective randomized study. It is well accepted that patients in clinical studies perform better than in the real world. Although we cannot conclude that all elderly patients should be treated with an aggressive approach, we do encourage patients, regardless of age, to be considered for combined modality therapy tailored to their specific medical situation. Our results are reassuring in that elderly patients who were deemed clinically fit benefited from the addition of durvalumab with substantial survival gains. The associated treatment risks were also acceptable. Our robust follow-up and toxicity data also provide valuable information on clinical management in elderly patients. Future studies should focus on appropriate identification and optimization of elderly patients so that curative-intent therapy can be safely delivered.

In summary, well-selected elderly patients with unresectable stage III NSCLC can be safely treated with CRT followed by durvalumab with similar survival benefits compared with their younger counterparts. We would strongly advocate for the referral of all patients for oncologic assessment to avoid undertreatment of elderly patients.

**CRediT Authorship Contribution Statement**

**Sally C. M. Lau:** Conceptualization, Writing – original draft.

**Malcolm Ryan:** Data curation.

**Jessica Weiss:** Formal analysis.

**Aline Fusco Fares:** Conceptualization.

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Sabine Schmid, Shelley Kuang: Data curation, Writing – review & editing.

Adrian G. Sacher: Writing – review & editing, Supervision.

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