# Sex Differences in Presentation, Treatment and Survival in Patients Receiving Palliative (Chemo)Radiotherapy for Non-Small Cell Lung Cancer

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**Abstract.** Background/Aim: The aim of this study was to analyze sex differences in a real-world cohort of patients who received palliative thoracic radiotherapy or chemoradiotherapy for non-small cell lung cancer. Materials and Methods: Retrospectively, baseline, treatment, toxicity and survival data from a single institution were analyzed. The study included 181 patients (82 females, 99 males). Results: Despite borderline significant differences in disease presentation (T and N stage), final assignment to stage II, III or IV was similar. The same was true for target volume size. Neither radiotherapy parameters nor systemic treatment approaches were significantly different. Toxicity profiles and survival were similar too. Less than 1 out of 3 patients experienced high-grade toxicity, largely esophagitis. Median survival was 8.1 (males) versus 7.8 months (females) and the corresponding 2-year survival rates were 16 and 15%, respectively ($p$=0.78). Conclusion: Relevant sex differences were not observed in this study of common radiotherapy regimes such as 10 fractions of 3 Gy or 15 fractions of 2.8 Gy, the latter often combined with carboplatin/vinorelbine chemotherapy.

Treatment algorithms for non-small cell lung cancer (NSCLC) not amenable to curative approaches such as surgical resection, stereotactic ablative radiotherapy or chemoradiotherapy, *i.e.*, a considerable proportion of patients with disease in stage IIIB or higher, have evolved due to introduction of several new targeted agents and immune checkpoint inhibitors (ICI) (1-4). A subgroup of patients continues to receive palliative (chemo)radiotherapy, e.g., for stage IV disease with predominantly thoracic disease burden and related clinical symptoms or for stage IIIB disease where standard chemoradiotherapy to 60-66 Gy is unfeasible due to comorbidity, unacceptable radiation dose to critical normal tissues or patient preference (5, 6).

It has been suggested that sex differences exist in risk of severe adverse events in patients receiving immunotherapy, targeted therapy, or chemotherapy in cancer clinical trials (7). Sex might also be associated with the outcome of patients treated with radiation for NSCLC (8). In the latter study, women were significantly more likely to have earlier stage disease, to have smoked <50 pack-years, and to have adenocarcinoma or large-cell carcinoma. For each stage, treatment did not differ between women and men. Five-year survival rates were significantly better for women than for men (28.6% versus 16.1%). The same was true regarding disease-free survival (31.2% versus 20.1%). In the subgroup of patients with medically inoperable stage I NSCLC, women had significantly improved 5-year survival compared with men (30.0% versus 13.1%). On multivariate analysis, male sex, weight loss, age ≥65 years, and stage III disease were found to be associated with poorer survival.

Such data has stimulated interest in gender-dependent radiotherapy as a component of personalized oncology (9). So far, there is a paucity of comparative studies in

patients with more advanced NSCLC who receive palliative (chemo)radiotherapy. Therefore, the present study was performed.

## Patients and Methods

This was a secondary, retrospective analysis of an institutional quality-of-care database, which is maintained and updated each year at Nordland Hospital Trust. Treatment consisted of palliative 3-dimensional conformal radiotherapy or chemoradiotherapy and was administered between 2009 and 2021. We included all patients with a prescribed total dose of 30-54 Gy, and excluded those with low-dose radiotherapy, primarily 2 fractions of 8.5 Gy. Chemoradiotherapy employed the Norwegian CONRAD regime (15 fractions of 2.8 Gy, 4 cycles of carboplatin/vinorelbine before and during radiotherapy) [10]. Follow-up data was abstracted from our electronic patient record system, including serious radiation-related toxicity and survival. The system captures hospitalization at all other hospitals in our healthcare region (northern Norway), thus providing complete and comprehensive data. After the first follow-up visit at 6-8 weeks from the final radiotherapy session, intervals were increased to 3 months. Local control and progression-free survival were not assessed in a systematic and evaluable manner. Treatment plans were calculated with Varian Eclipse TPS®. IBM SPSS v.28 was employed for statistical analyses (IBM Corp., Armonk, NY, USA). The latter included 2-tailed Fisher exact probability tests, chi-square and t-tests, and actuarial overall survival analysis (Kaplan-Meier method; log-rank test). At the time of analysis in 2023, 20 patients (11%) were alive (censored observations after a median follow-up of 34 months). Date of death was known for all remaining patients.

## Results

The study included 82 female and 99 male patients, 6 (3%) of whom had failed to complete the prescribed course of radiotherapy. Females and males had identical median age (70 years, Table I). Similar distributions were observed for most baseline characteristics including smoking history, diagnosis of chronic obstructive pulmonary disease and tumor histology. Borderline significant differences ($p$=0.04 and 0.06, respectively) were observed for T and N stage ($7^{th}$ edition (11)), which eventually did not influence the overall stage distribution. Stage III was present in 44 and 45%, respectively (stage IV: 51 and 47%, respectively).

Treatment-related disparities were not identified, *e.g.*, regarding radiation dose/fractionation, concomitant therapy utilization, preceding and subsequent systemic therapy (Table I). Radiation target volume size and resulting dosimetric parameters, *e.g.*, for lung and esophageal dose were not significantly different (Table II). Selected toxicity outcomes of interest were similar, too (Table III). Less than 1 out of 3 patients experienced high-grade toxicity. We did not analyze typical low-grade toxicities such as temporary nausea or skin reactions. Hematological toxicity was not available either.

Median overall survival was 8.1 (males) versus 7.8 months (females) and the corresponding 2-year survival rates were 16 and 15%, respectively ($p$=0.78).

## Discussion

In continuation of previous quality-of-care studies from our department (3, 4, 12), we analyzed sex differences in 181 patients receiving palliative (chemo)radiotherapy for

NSCLC. A previous end-of-life care analysis in a less restricted patient population managed with or without radiotherapy (sometimes primary best supportive care, sometimes systemic therapy alone) has shown that initial sex differences did not persist in multivariable analysis (13). During the last 3 months of life, female patients spent significantly more days in hospital than their male counterparts. Place of death was not significantly different. Home death was equally uncommon in each group. In the multivariable analysis, survival was associated with age and cancer stage, in contrast to sex. The present study in irradiated patients confirmed that relevant sex differences in presentation, treatment, selected toxicity endpoints and survival did not exist.

A large-scale analysis of treatment-related adverse events by sex in Southwest Oncology Group (SWOG) phase II and III clinical trials conducted between 1980 and 2019, excluding sex-specific cancers, was reported in 2022 (7). The Common Terminology Criteria for Adverse Events were utilized. Multivariable logistic regression was used, adjusting for age, race, and disease prognosis. Thirteen symptomatic and 14 objective adverse event categories were examined in 23,296 patients. Of these, 17,417 received chemotherapy, 2,319 received immunotherapy, and 3,560 received targeted therapy. Overall, 64.6% experienced one or more severe (grade ≥ 3) adverse event. Interestingly, females had a 34% increased risk of severe adverse events compared with males (95% confidence interval, 1.27 to 1.42, $p<0.001$). Women experienced an increased risk of severe symptomatic adverse events among all treatments. In particular, female patients managed with chemotherapy or immunotherapy experienced increased severe hematologic toxicity. No statistically

significant sex differences in risk of non-hematologic side effects were found. Our own study focused on radiotherapy and did therefore not include hematologic toxicity.

Other radiotherapy studies suggested potential correlations between sex and certain types of toxicity. For example, female patients had a greater risk of rib fracture than male patients after stereotactic lung irradiation (hazard ratio = 0.59; 95% CI, 0.46-0.76) (14). Comparable findings were reported for radiation esophagitis (15-17). Inconsistent survival results were observed in previous studies of thoracic radiotherapy for NSCLC, typically in the curative setting. In one study, 5-year survival rates were significantly better for women than for men (28.6% versus 16.1%). On multivariate analysis, male sex, weight loss, age ≥65 years, and stage III disease were found to be associated with poorer survival (8). Comparable data were reported by others (18). For stereotactic body radiotherapy, male patients had poorer survival too (19). However, not all studies reported sex-related survival differences after curative radiotherapy, a prominent example being the multicentre UK CHART analysis (20). In a nationwide Swedish population-based cohort study, men with NSCLC had a consistently poorer prognosis, even after careful adjustments for a wide range of prognostic factors (21). While the pattern was similar in both squamous cell and adenocarcinoma, it was larger and more consistent in the latter. The fact that men with NSCLC have a poorer prognosis was also observed in other countries such as Japan (22) and Australia (23).

In the palliative radiotherapy setting examined in our study, survival was not influenced by sex, a finding previously also reported from the UK (24). Possibly, other major prognostic factors such as patterns and total burden of metastases, weight loss, poor performance status etc. outweigh the impact of sex that has been reported in other

settings or population-based registries. Interestingly, despite interest in gender-dependent radiotherapy resulting in ongoing research projects, numerous recent guidelines (lung cancer and other types) did not stratify recommendations by sex (25-30).

The limitations of our study include its single-institution methodology, size, and absence of certain toxicity data as well as local control and progression-free survival. Nevertheless, it represents a real-world experience from a region where adherence to national treatment guidelines is high and continuous monitoring of quality-of-care takes place (3, 4). In clinical practice, we are currently paying more attention to age, frailty, organ function, comorbidity and social support than sex.

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## Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study. SGA is investigator in the Astra Zeneca PACIFIC 8 trial and has received lecture fees from Merck.

**Table I. Baseline characteristics in 181 patients, stratified by sex (82 females, 99 males).**

| Parameter | n (females) | % (females) | n (males) | % (males) | *p*-value |
|---|---|---|---|---|---|
| Tumor stage | | | | | 0.77 |
| II | 4 | 5 | 7 | 7 | |
| III | 36 | 44 | 45 | 45 | |
| IV | 42 | 51 | 47 | 47 | |
| Primary tumor (T) stage | | | | | 0.04 |
| T1 or absent after surgical removal | 19 | 23 | 9 | 9 | |
| T2 | 13 | 16 | 26 | 26 | |
| T3 | 30 | 37 | 37 | 37 | |
| T4 | 20 | 24 | 27 | 27 | |
| Thoracic lymph node metastases (N) stage | | | | | 0.06 |
| N0 | 12 | 15 | 19 | 19 | |
| N1 | 3 | 4 | 13 | 13 | |
| N2 | 37 | 45 | 43 | 43 | |
| N3 | 30 | 37 | 24 | 24 | |
| Histology | | | | | 0.98 |
| Adenocarcinoma | 37 | 45 | 41 | 41 | |
| Squamous cell carcinoma | 34 | 41 | 42 | 42 | |
| Large cell carcinoma | 6 | 7 | 8 | 8 | |
| Unspecified/mixed/others | 5 | 6 | 8 | 8 | |

| | | | | | |
|---|---|---|---|---|---|
| Site | | | | | 0.46 |
| Left lung | 22 | 27 | 37 | 37 | |
| Right lung | 44 | 54 | 48 | 48 | |
| Both lungs | 4 | 5 | 3 | 3 | |
| Mediastinum only | 12 | 15 | 11 | 11 | |
| Smoking history | | | | | 0.73 |
| Never | 3 | 4 | 5 | 5 | |
| Previous | 62 | 76 | 70 | 70 | |
| Active | 17 | 21 | 24 | 24 | |
| Treatment | | | | | 0.75 |
| Concurrent chemoradiotherapy | 26 | 32 | 29 | 29 | |
| Systemic non-concurrent treatment | | | | | 0.68 |
| Within 4 weeks before radiotherapy | 36 | 44 | 38 | 38 | |
| Earlier than 4 weeks before radiotherapy | 11 | 13 | 17 | 17 | |
| No preceding treatment | 35 | 43 | 44 | 44 | |
| Post-radiation systemic treatment | | | | | 0.65 |
| Did receive additional treatment | 38 | 46 | 50 | 50 | |
| Radiotherapy dose category | | | | | 0.69 |
| Low such as 10 fractions of 3 Gy | 25 | 30 | 32 | 32 | |
| Intermediate such as 12 fractions of 3 Gy | 21 | 26 | 20 | 20 | |
| High such as 15 fractions of 2.8-3 Gy | 36 | 44 | 47 | 47 | |

| | | | | | |
|---|---|---|---|---|---|
| Radiotherapy fraction number | | | | | 0.81 |
| <10 | 3 | 4 | 4 | 4 | |
| 10 | 30 | 37 | 38 | 38 | |
| >10 | 49 | 60 | 57 | 57 | |
| Radiotherapy dose per fraction | | | | | 0.12 |
| <3 Gy | 23 | 28 | 42 | 42 | |
| 3 Gy | 48 | 59 | 48 | 48 | |
| >3 Gy | 11 | 13 | 9 | 9 | |
| Comorbidity | | | | | |
| Chronic obstructive pulmonary disease | 25 | 30 | 29 | 29 | 0.87 |
| Age | | | | | |
| Median age, range (years) | 70 | 53-88 | 70 | 41-90 | 0.57 |

**Table II. Radiotherapy parameters in 181 patients, stratified by sex (82 females, 99 males).**

| Parameter | females | females | males | males | *p*-value |
|---|---|---|---|---|---|
| Median clinical target volume size, range (ccm) | 112 | 21-860 | 129 | 10-1185 | 0.73 |
| Median planning target volume size, range (ccm) | 369 | 95-1272 | 389 | 104-1950 | 0.60 |
| Median mean lung dose, range (Gy) | 10.4 | 3-19 | 8.6 | 1-21 | 0.36 |
| Median lung V20 (volume exposed to 20 Gy), range (%) | 20.5 | 5-40 | 18.0 | 2-47 | 0.67 |
| Median maximum dose to the heart, range (Gy) | 24.2 | 9-58 | 26.4 | 0-50 | 0.84 |
| Median maximum dose to the esophagus, range (Gy) | 39.8 | 2-47 | 36.5 | 1-52 | 0.43 |
| Median mean dose to the esophagus, range (Gy) | 14.9 | 1-43 | 15.0 | 1-37 | 0.93 |
| Median esophagus V20, range (%) | 42 | 0-80 | 34 | 0-87 | 0.85 |

**Table III. Toxicity data in 171 patients, stratified by sex (77 females, 94 males). Exclusion of patients who did not complete radiotherapy due to rapid disease progression or died before toxicity was observed. Observation period: initial 3 months.**

| Parameter | n (females) | % (females) | n (males) | % (males) | *p*-value |
|---|---|---|---|---|---|
| Esophageal toxicity-free | 53 | 69 | 60 | 64 | |
| Esophageal toxicity grade 1 | 5 | 6 | 10 | 11 | |
| Esophageal toxicity grade 2 or higher | 19 | 25 | 24 | 26 | 0.64 |
| Hospitalized for cardiopulmonary toxicity | 3 | 4 | 2 | 2 | 0.66 |