Survival and Pulmonary Toxicity in Non-Small Cell Lung Cancer : The Role of Pre-Treatment GTV Volume and Dosimetric parameters

Abstract :

Objective: To evaluate the impact of gross tumor volume (GTV) on overall survival (OS) and acute pulmonary toxicity in patients with non-small cell lung cancer (NSCLC) treated with three-dimensional conformal radiotherapy (3D-CRT).

Methods: We retrospectively analyzed clinical and dosimetric data from 65 patients treated at the Radiation Oncology Department of Hassan II University Hospital, Fez, between January 2012 and July 2022. Survival outcomes were assessed using Kaplan-Meier method. Survival according to GTV volume was analyzed using the Log-rank test, while associations between acute pulmonary toxicity and variables such as age >65 years, GTV volume, MLD, V20Gy, and V30Gy were assessed using the Chi-squared test, with statistical significance set at $p \leq 0.05$

Results: The mean OS was 22.8 months. Median overall survival was 21 months for patients with GTV volume< 100 cc and 14 months for those with GTV volume $\geq$ 100 cc, with a non-significant trend favoring smaller tumors (p = 0.059). Acute pulmonary toxicity was significantly associated with MLD >20 Gy, V20Gy>30%, and V30Gy>20% (p=0.0001).

22   **Conclusion:** Smaller GTV volumes were associated with improved survival.

23   Dosimetric parameters were predictive of pulmonary toxicity, highlighting the

24   importance of individualized treatment planning.

25   **Keywords:** Gross tumor volume, NSCLC, radiotherapy, survival, pulmonary

26   toxicity, dosimetric parameters.

27

Introduction

Three-dimensional conformal radiotherapy (3D-CRT) enables radiation oncologists to define target volumes more precisely, select optimal beam angles, and tailor dose distributions compared to previous techniques. Several radiotherapy (RT) parameters have been explored for their potential link to survival outcomes (1).

Tumor volume and the total dose of radiation are among the factors that have shown a direct impact on survival and clinical outcomes. Numerous studies have demonstrated a negative correlation between tumor volume and survival, with tumor size emerging as a more important prognostic factor than T-stage (1, 2, 3, 4).

The size of the primary tumor has also been found to correlate with survival in patients with stages I-III non-small-cell lung cancer (NSCLC). Patients with larger tumor volumes tend to have a worse prognosis compared to those with smaller volumes, even though long-term survival can still be achieved with an appropriately prescribed radiation dose (5, 6). These findings support the hypothesis that tumor volume significantly affects radiotherapy outcomes (3.7). Furthermore, the impact of primary tumor volume on survival has been explored in advanced-stage NSCLC, including stage IV, with smaller tumor volumes often associated with better outcomes (8.9). Considering the strong correlation between tumor volume and survival, incorporating the gross tumor volume (GTV) into the TNM staging system could provide a more accurate prognostic assessment.

51 Regarding radiation dose, larger tumor volumes typically receive lower doses to

52 minimize toxicity, and chemoradiotherapy has been associated with increased

53 lung and esophageal toxicity compared to radiation alone. Parameters derived

54 from dose-volume histograms (DVH) are being studied for their role in lung

55 toxicity development (1).

56 This study aims to assess whether GTV volume can predict survival outcomes

57 and whether dosimetric factors correlate with the risk of acute pulmonary

58 toxicity in patients with inoperable NSCLC undergoing 3D-CRT.

59

60 **Materials and Methods**

61 **Design of Study and Eligibility:** This retrospective, analytical, monocentric

62 study was conducted at the Radiotherapy Department of CHU HASSAN II, Fez. It

63 was approved by the Ethics Committee of the Hassan II University Hospital in

64 Fez. Informed consent was obtained from all participants involved in the study.

65 All patient data were anonymized to ensure confidentiality and privacy.

66 The clinical and dosimetric records of patients with non-small-cell lung cancer

67 (NSCLC) were reviewed. Between January 2012 and July 2022, 65 patients

68 treated with three-dimensional conformal radiotherapy (3D-CRT) for locally

69 advanced NSCLC with curative intent were retrospectively analyzed. All patients

70 had biopsy-proven NSCLC. Only patients with complete and exploitable clinical

71 and dosimetric records were included in the study.

72 Patients were eligible if they had a confirmed diagnosis of NSCLC through biopsy

73 and received 3D-CRT with curative intent. Only those followed up at the

74 Radiotherapy Department of CHU HASSAN II, Fez, with complete and usable

75 records, were included in the study. Patients were excluded if they were treated

76 with palliative intent, had incomplete or non-exploitable records, or were treated

77 outside CHU HASSAN II, Fez.

78

79 **Data Collection:** Data were collected using a pre-established exploitation form

80 based on medical records from the hospital network database, Hosixnet, as well

81 as the ARIA Treatment Planning System (TPS).

82

83 **Gross tumor volume (GTV)** : The gross tumor volume (GTV), or macroscopic

84 tumor volume, was delineated according to ICRU reports 50 and 62, and

85 determined through endoscopy and imaging techniques such as CT scan, MRI, or

86 PET scan.

87 The primary tumor was contoured using pulmonary CT windows. Mediastinal

88 adenopathies were contoured separately using mediastinal windows. GTV and

89 PTV were determined using the dose-planning system based on the CT data set.

90

91 **Dosimetric Parameters Analyzed:** The dosimetric parameters analyzed

92 included the GTV volume in cm^3, the Mean Lung Dose (MLD) in Gray, and the

93 lung volume receiving 20 Gy (V20Gy) and 30 Gy (V30Gy).

94

95 **Acute Pulmonary Toxicity:** Acute pulmonary toxicity was assessed by the

96 radiation oncologist during weekly follow-up consultations and up to three

97 months after the end of treatment. Toxicity was graded according to the

98 Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

99

100 **Statistical Analysis:**

Statistical analysis was performed using IBM SPSS Statistics version 25. Overall survival was calculated using Kaplan-Meier curves. Overall survival was measured from the date of diagnosis until the date of the last follow-up or death, and estimated using the Kaplan-Meier method.

The Log-rank test was used to analyze survival in relation to the volume of the GTV. The Chi-squared test (Chi-2) was used to analyze variables significantly associated with acute pulmonary toxicity, including age greater than 65 years, GTV volume, Mean Lung Dose (MLD), V20Gy, and V30Gy. In cases where the expected cell counts were less than 5, Fisher's exact test was applied to ensure statistical validity. A p-value ≤ 0.05 was considered statistically significant.

Results

1. Patient Characteristics

The data summarized in Table 1 provide an overview of the key patient characteristics, including age, sex, histology, smoking status, AJCC staging, and treatment protocols.

A total of 65 patients were included in the study, with a median follow-up of 16.03 months. The mean age at diagnosis was 61 years (range: 39 to 81 years). The majority of patients were male (58 men, 89%) compared to 7 women (11%), yielding a sex ratio of 8.3. Most patients (84.61%, n=55) reported a history of smoking.

Histologically, the population was nearly equally divided between adenocarcinoma (n=33; 50.61%) and squamous cell carcinoma (n=32; 49.39%). Regarding staging according to the AJCC 8th edition (2017), only one patient (1.23%) was diagnosed at stage IB. Stage II was found in 11 patients (16.92%),

125   divided into stage IIA (n=4; 6.15%) and stage IIB (n=7; 10.77%). The majority

126   were diagnosed at stage III (n=53; 81.53%), subdivided into stage IIIA (n=16;

127   30.18%), IIIB (n=29; 54.71%) and IIIC (n=8; 15.09%).

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129 **<u>Table 1: Patient demographics and tumor characteristics</u>**

Characteristics	Distribution (%)
Mean Age	61 years, range39-81 years
Male/Female	89/11 (58/7)
Histology	
▪ Adenocarcinoma	50.61
▪ Suquamous cell carcinoma	49.39
Smoking :	84.61
AJCC Stage at Diagnosis:	
I	1.23
▪ **IB**	1.23
II	16.92
▪ **IIA**	18.18
▪ **IIB**	21.95
III	81.53
▪ **IIIA**	30.18
▪ **IIIB**	54.71
▪ **IIIC**	15.09
Treatment protocol	
▪ Induction chemotherapy followed by 3D-CRT	38.46
▪ Concomitant Chemoradiotherapy	49.23
▪ Exclusive radiotherapy	12.3

130

2. Treatment details

As presented in **Table 2**, 25 patients (38.46%) received induction chemotherapy followed by 3D-conformal radiotherapy (3D-CRT), 32 patients (49.23%) underwent concurrent chemoradiotherapy, and 8 patients (12.3%) received exclusive radiotherapy.

The mean total radiation dose was 63.2 Gy (range: 44 to 66 Gy), with a dose per fraction ranging from 2 to 2.75 Gy. Treatment duration ranged from 3 to 7 weeks. Among those who received induction chemotherapy, the most frequently used regimen was cisplatin + Navelbine (n=15; 58%), followed by carboplatin + paclitaxel (n=7; 29%), carboplatin + gemcitabine (n=2; 9.67%), and cisplatin + etoposide (n=1; 3.22%).

For concurrent chemotherapy, cisplatin + vinorelbine was used in 66.66% of patients, while carboplatin + paclitaxel was used in 18.84%.cisplatin was administered at a dose of 80 mg/m² on days 1 and 8, along with vinorelbine at 15 mg/m² on days 1 and 8, with a 21-day interval. Another regimen involved carboplatin with AUC 2 on days 1, 8, and 15, and paclitaxel at a dose of 45 mg/m² on days 1, 8, and 15, also with a 21-day interval. Regarding concurrent chemoradiotherapy, 66.66% of patients received cisplatin + Vinorelbine, and 18.84% received carboplatin + paclitaxel.

151 **Table 2: Radiotherapy and Chemotherapy Treatment Protocols**

| Characteristics	Distribution (%)
Radiotherapy:	
·Average total dose (DT)	63,2 Gy (44-66Gy)
·Dose per fraction	2-2,75Gy
·Treatment duration	3-7 weeks
Chemotherapies used	
·Induction:	
OCisplatin-Navelbine	58%
OCarboplatin-Paclitaxel	29%
OCarboplatin-Gemcitabine	9,67%
OCisplatin-Etoposide	3,22%
·Concurrent:	66,66%
OCisplatin + vinorelbine	
OCarboplatin + Paclitaxel	18,84%

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3. GTV Volume Analysis

The mean gross tumor volume (GTV) was 258 cm^3, with a wide range from 6.6 to 899 cm^3. As shown in **Figure 1,** for tumors within the same stage (stage III), large inter-individual variability in volume was observed (e.g., two stage III patients: 134 cm^3 vs. 416 cm^3).
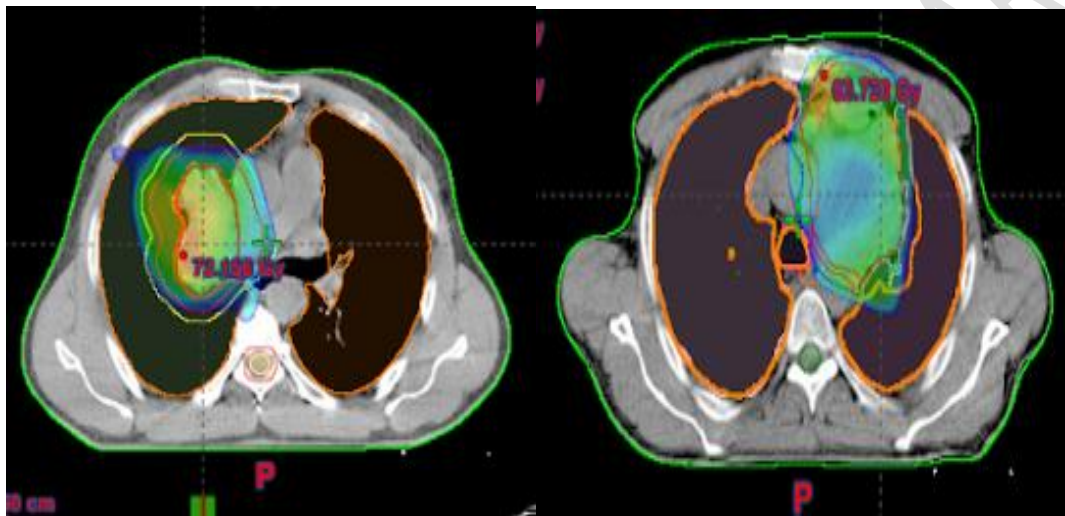
Figure.1 Example of intra-stage variation in GTV for two stage III patients (T4N0: 134 cm^3 vs T4N2: 416 cm^3).

4. Overall Survival Based on GTV Volume

The mean overall survival for the cohort was 22.78 months (95% CI: 17.31–28.25 months)(**Figure 2, Annex A6)**.

Fonction de survie
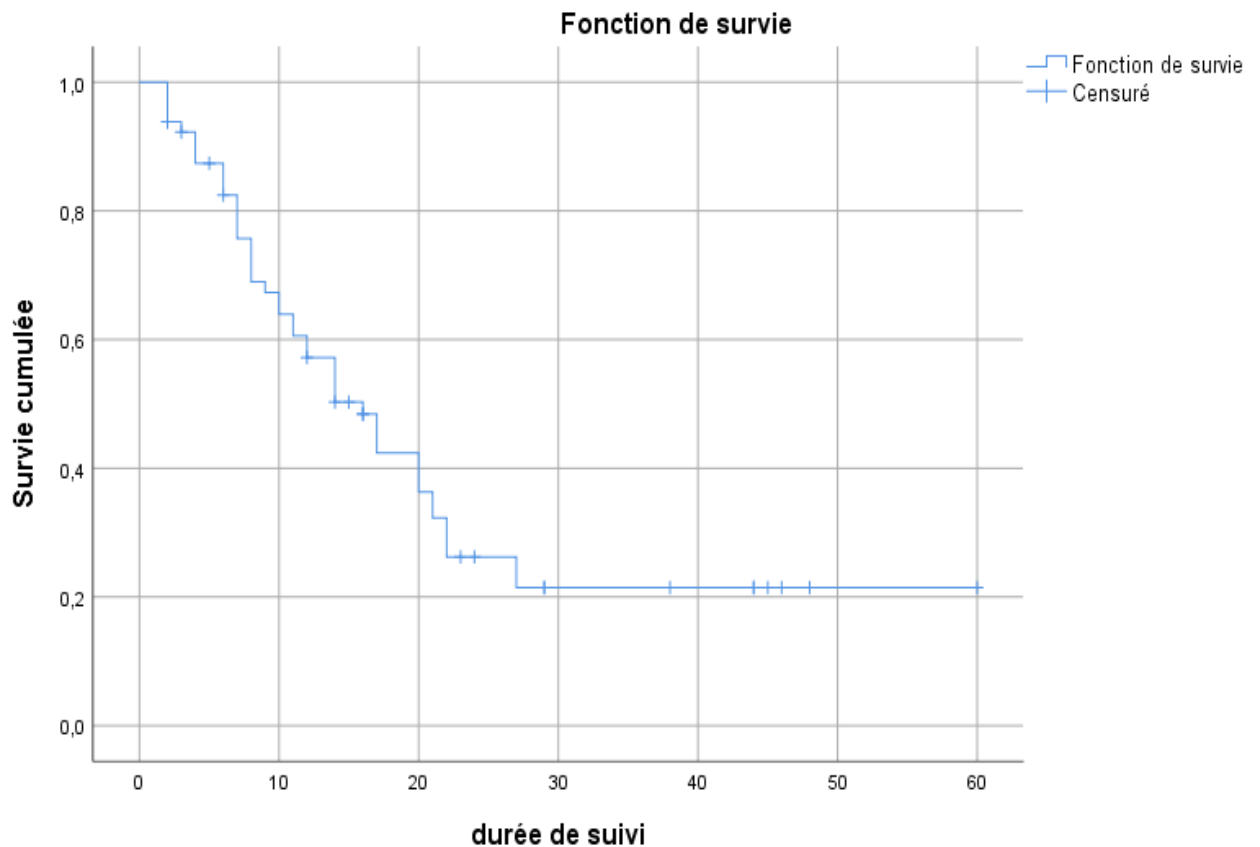
165   **Figure.2 Overall survival using Kaplan–Meier curves**

166   Median overall survival was 21 months (95% CI: 11.15–30.85) for patients with

167   GTV volume< 100 cc, compared to 14 months (95% CI: 7.31–20.69) for those

168   with GTV volume ≥ 100 cc (Figure 2).

169   Although the difference did not reach statistical significance (Log-rank test, p =

170   0.059), there was a trend toward improved survival in patients with smaller

171   tumor volumes (**Figure 3**).
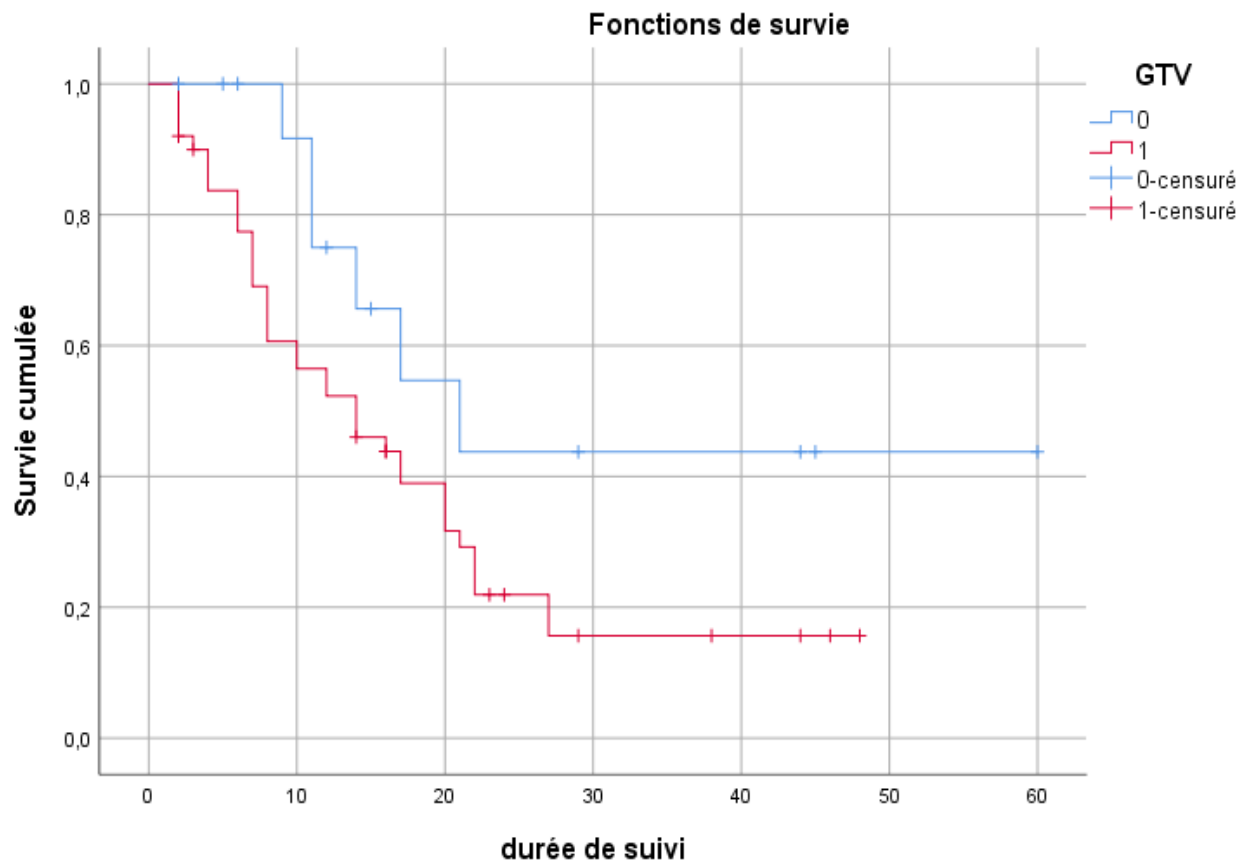
Figure.3Overall survival according to GTV volume (cm^3) assessed by the log-rank test.

Detailed descriptive statistics including means, medians, standard errors,95% confidence intervals for survival times and the global comparison of survival curves by Log-rank test are summarized in **Annex A7**.

5. Acute Pulmonary Toxicity and Dosimetric Parameters

Acute pulmonary toxicity was observed in 20 out of 65 patients (30.76%). The clinical presentation consisted of dry cough in 55% of cases (n=11) and dyspnea in 45% (n=9).

13

182   Regarding the dosimetric parameters, the mean Mean Lung Dose (MLD) was

183   14.32 Gy (range: 2.7 to 33 Gy). The average lung volume receiving at least 20 Gy

184   (V20Gy) and 30 Gy (V30Gy) was 17.52% (range: 3.4-46.3%) and 23% (range: 3-

185   39%), respectively.

186   We performed Chi-squared tests to assess the association between acute

187   pulmonary toxicity and several clinical and dosimetric parameters. The results

188   are summarized in Annexes A1 to A5.

189   **1. Age ≥60 years**

190   There was no statistically significant association between age and acute

191   pulmonary toxicity. Among patients aged under 60 years, 32% developed

192   toxicity, compared to 30% in those aged ≥60 years (p = 0.865).

193   (See **Annex A2**, Table A2)

194   **2. GTV Volume >100 cc**

195   The analysis showed no significant relationship between GTV volume and acute

196   pulmonary toxicity (p = 0.377). However, the toxicity rate appeared slightly

197   higher in patients with GTV <100 cc (40%) compared to those with GTV >100 cc

198   (28%).

199   (See **Annex A1**, Table A1)

200   **3. Mean Lung Dose (MLD) >20 Gy**

201   A statistically significant association was observed between MLD >20 Gy and

202   acute pulmonary toxicity (p < 0.001). Among patients with MLD >20 Gy, 88.9%

203   experienced acute toxicity, versus only 21.4% in those with MLD <20 Gy.

204   (See **Annex A3**, Table A3)

205   **4. V20Gy >30%**

206   There was a strong and statistically significant correlation between V20Gy >30%

207   and acute pulmonary toxicity ($p < 0.001$). Toxicity was reported in 93.3% of

208   patients with V20Gy >30%, compared to 12% for those below this threshold.

209   (See **Annex A4**, Table A4)

210   **5. V30Gy >20%**

211   Similarly, a significant correlation was found between V30Gy >20% and toxicity

212   ($p < 0.001$). Among patients with V30Gy >20%, 75% developed acute toxicity,

213   compared to only 11.1% when V30Gy was <20%.

214   (See **Annex A5**, Table A5)

215   These findings support the predictive value of certain dosimetric parameters

216   (MLD, V20Gy, V30Gy) for pulmonary toxicity, while demographic and volumetric

217   factors (age, GTV) did not reach statistical significance.

218   # **Discussion**

219   Chemoradiotherapy, whether concurrent or sequential, is regarded as the

220   standard first-line treatment for locally advanced nonresectable NSCLC patients

221   with good performance status (10). However, the TNM staging system alone is

222   not sufficient to predict the outcomes of radiotherapy or chemoradiotherapy in

223   such cases (1–4). While tumor volume has been widely shown to have a stronger

224 correlation with survival and clinical outcomes than TNM stage in this context,

225 appropriate prognostic cut-offs have yet to be established.

226 Our data indicate that a high pre-RT gross tumor volume (GTV) is associated

227 with inferior overall survival (OS). This aligns with large datasets evaluating pre-

228 treatment GTV and its impact on outcomes after RT, such as the study by Bradley

229 et al. (3), who reported a strong influence of baseline GTV before RT on OS,

230 cause-specific survival, and tumor control. They made a very accurate

231 stratification, identifying five prognostic classes based on GTV among 207 stage

232 I-IIIB NSCLC patients treated with definitive RT: GTV <25 cm^3, 25-60 cm^3, 60-

233 110 cm^3, 110-180 cm^3, and >180 cm^3. Ninety-five patients with stage III disease

234 received chemotherapy, but further stratification by GTV in this subgroup was

235 not reported.

236 Similarly, Etiz et al. (4) found that among 150 patients treated with RT, GTV (<80

237 cm^3) was the most powerful independent predictor of survival, while N-stage

238 (N0 vs N1-3) was only associated with time to progression (TTP). Even in the

239 111 patients with stage III disease in this study, GTV was the best predictor of

240 survival.

241 Martel et al. (2) identified GTV (<200 cm^3) as a predictor of survival among 76

242 patients with stage I-IIIB disease, though the cut-off rationale was not described,

243 and GTV lost significance in multivariate analysis when stage IIIB, nodal

244 involvement, and age >65 years were considered.

245   Willner et al. (5) examined 135 patients at any stage (I–IV) and found GTV was

246   significantly related to survival when stratified into three classes: <100 cm^3, 100-

247   200 cm^3, and >200 cm^3. Finally, Werner-Wasik et al. (11) found that a GTV <63

248   cm^3 was a predictor of OS in 22 patients, most with stage III disease receiving

249   chemotherapy in addition to thoracic RT.

250   A recent study by Xiaxia Chen et al. (2024) investigated the impact of GTV

251   volume on the survival of patients with stage IV non-small cell lung cancer

252   (NSCLC) treated with three-dimensional (3D) radiotherapy. The results showed

253   that patients with a GTV of less than 150 cm^3 had significantly longer survival

254   compared to those with a GTV greater than 150 cm^3. Multivariate analysis

255   identified favorable prognostic factors, including peripheral lung cancer, a

256   radiation dose of ≥63 Gy, and 4 to 6 cycles of chemotherapy.

257   The study further demonstrated that with 2 to 3 cycles of chemotherapy

258   concurrent with 3D radiotherapy, patients with a GTV <150 cm^3 experienced

259   better survival outcomes compared to those with a GTV ≥150 cm^3 (p<0.05).

260   These findings underscore the importance of considering tumor volume in

261   treatment planning to improve survival in stage IV NSCLC patients (**12**).

262   Our study also confirmed the importanceof GTV volume in predicting survival

263   outcomes. The mean GTV in our cohort was 258 cm^3, with extremes ranging

264   from 6.6 to 899 cm^3. Interestingly, we observed significant variations in tumor

265   volumes even among patients with the same clinical stage. For instance, one

266   patient with a T4N0 tumor had a GTV of 134 cm^3, while another with a T4N2

267   tumor had a GTV of 416 cm^3, as shown in Figure 1. This highlights the variability

268   in tumor burden even within the same stage and emphasizes the need for precise

269   volume-based stratification to guide treatment decisions.

270   Regarding toxicity, multivariate analyses in various studies have identified

271   numerous variables directly related to the development of moderate to severe

272   radiation pneumonitis (RP). These include patient characteristics, such as

273   performance status (PS), female gender, pre-treatment FEV1, PaO2 less than 80

274   mmHg (13), or ongoing tobacco use as a protective factor (5); the type and

275   schedule of concurrent chemotherapy (14–16); dose-volume histogram (DVH)

276   parameters such as mean lung dose (MLD) (2.17.18), V20Gy (16.19.20), or

277   V30Gy (21); radiation field size in series not using 3D RT (13); and theoretical

278   models like normal tissue complication probability (NTCP) (2.17.18. 21 .22).

279   In all series, the addition of chemotherapy to radiation, particularly in the

280   concurrent setting, seems to increase the risk of developing RP.

281   However, variability in toxicity grading systems (e.g., SWOG, RTOG, CTCAE) and

282   in lung volume analysis methods may influence reported RP incidence

283   (16.17.19).

284   In our study, we scored RP according to the 4th version of the CTCAE, which

285   covers a wide range of pulmonary toxicities, including specific categories for

286   radiation pneumonitis and other pulmonary complications. We also analyzed

287   lungs as two separate organs, optimizing dose distribution, minimizing

288 complications, and improving outcomes based on individual lung characteristics

289 and tumor location.

290 In our study, acute pulmonary toxicity was observed in 30.76% of patients, with

291 dry cough and dyspnea being the most common symptoms. Regarding

292 dosimetric parameters, we found that the mean lung dose (MLD) was 14.32 Gy

293 (range: 2.7-33 Gy). Additionally, the volume of lung receiving 20 Gy (V20Gy) and

294 30 Gy (V30Gy) had a significant correlation with toxicity. Specifically, the mean

295 volume of lung receiving 20 Gy (V20Gy) was 17.52% (range: 3.4-46.3%), and for

296 V30Gy, it was 23% (range: 3-39%). These findings underline the importance of

297 considering these dosimetric factors when planning treatment, as they correlate

298 strongly with the development of pulmonary toxicity.

299 A meta-analysis by Roach et al. (23) on over 1900 patients undergoing

300 chemoradiation therapy for NSCLC and SCLC identified total radiation dose >55

301 Gy and daily dose per fraction >2.67 Gy as key risk factors for RP. As total

302 radiation dose correlates with survival and clinical outcome, efforts have been

303 made to define the optimal dose considering higher toxicity with combined

304 treatment compared to radiation or chemotherapy alone, especially concerning

305 lung toxicity.

306   The advent of 3D-CRT has allowed the evaluation and correlation of numerous

307 variables with toxicity to help radiation oncologists prevent this dose-limiting

308 complication.

309   In our study, all evaluated DVH parameters, including MLD, V20Gy, and V30Gy,

310   were independent predictors of developing radiation pneumonitis, which aligns

311   with previous literature.

312   In addition to the findings from our study, a retrospective study by Nai-bin Chen

313   et al. (24) (Radiation Oncology, 2020) aimed to develop and validate a new

314   stratification system incorporating GTV-TNM for locally advanced non-small-cell

315   lung cancer (NSCLC) treated with definitive 3D-conformal radiotherapy. The

316   study included 340 patients, stratified into three groups based on GTV: G1 (<70

317   cm^3), G2 (70-180 cm^3), and G3 (>180 cm^3), as well as by TNM stage. The study

318   demonstrated that a lower GTV-TNM group was associated with better overall

319   survival and progression-free survival (P<0.001). The prognostic value of this

320   GTV-TNM stratification system was validated by significant improvements in

321   AUC scores (0.636 vs. 0.570, P=0.027) and F1 scores (0.655 vs. 0.615, p<0.001).

322   This supports our findings that GTV volume plays a crucial role in survival

323   outcomes in locally advanced NSCLC.

324   Furthermore, treatment strategies for locally advanced, inoperable non-small

325   cell lung cancer (NSCLC) have seen rapid advancements in recent years. In the

326   management of unresectable stage III NSCLC, the combination of chemotherapy

327   and immunotherapy has shown a synergistic effect, improving both local and

328   distant tumor control. Current guidelines for unresectable stage III NSCLC

329   recommend chemotherapy followed by one year of immune checkpoint inhibitor

330   (ICI) consolidation therapy.

331   However, several challenges remain, and further research is needed to

332   determine the optimal timing for chemotherapy, radiation, and ICI

333   administration, as well as the role of targeted therapies. A significant clinical

334   hurdle in enhancing patient outcomes for advanced lung cancer is the

335   development of resistance to immune checkpoint inhibitors (25).

336   Our retrospective analysis excluded adjuvant PD-L1 immunotherapy with

337   durvalumab in stage III NSCLC post-chemoradiotherapy due to its unavailability

338   during the study period, precluding conclusions on the interaction between GTV

339   volume, survival, dosimetric parameters, and pulmonary toxicity during

340   radiotherapy and adjuvant immunotherapy.

341   Nonetheless, this study highlights the critical importance of GTV volume and

342   dosimetric parameters in predicting survival and the risk of radiation-induced

343   pulmonary toxicity, offering valuable insights for clinical practice in NSCLC

344   management.

345   Further prospective studies with larger sample sizes are needed to confirm these

346   results and refine predictive models for acute pulmonary toxicity and survival

347   outcomes.

348   **Conclusion**

349   This retrospective study highlights the association between pre-treatment GTV

350   volume and overall survival (OS) in non-small-cell lung cancer (NSCLC) patients

351   treated with three-dimensional conformal radiotherapy (3D-CRT). Patients with

352   smaller GTV volume (<100 cm^3) had better survival outcomes. Additionally,

353   acute pulmonary toxicity was significantly associated with dosimetric

354   parameters such as mean lung dose (MLD), V20Gy, and V30Gy, while no

355   correlation was found with GTV volume or patient age.

356   These findings reinforce the importance of considering GTV volume and

357   dosimetric parameters in treatment planning to optimize survival and minimize

358   lung toxicity.

359   Furthermore, it may be valuable to integrate GTV volume into the TNM staging

360   system to improve prognostic accuracy and guide treatment decisions. Future

361   studies should further explore the impact of combination therapeutic

362   approaches, including immunotherapy, on these factors.

363

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450

451 **Annexes**

452 **Table A1: Association Between Acute Pulmonary Toxicity and GTV Volume**

GTV volume	Toxicity No	Toxicity Yes	Row Total
< 100 cc	9 (60.0%)	6 (40.0%)	15 (100%)
> 100 cc	36 (72.0%)	14 (28.0%)	50 (100%)
Total	45 (69.2%)	20 (30.8%)	65 (100%)

453 Chi-squared: 0.780

454 $p = 0.377$

455 Fisher's exact $p = 0.524$

456 **Table A2: Association Between Acute Pulmonary Toxicity and Age**

Age	Toxicity No	Toxicity Yes	Row Total
< 60 years	17 (68.0%)	8 (32.0%)	25 (100%)
>= 60 years	28 (70.0%)	12 (30.0%)	40 (100%)
Total	45 (69.2%)	20 (30.8%)	65 (100%)

457 Chi-squared: 0.029

458 $p = 0.865$

459 Fisher's exact $p = 1.000$

460

461 **Table A3: Association Between Acute Pulmonary Toxicity and Mean Lung**
462 **Dose (MLD)**

MLD	Toxicity No	Toxicity Yes	Row Total
< 20 Gy	44 (78.6%)	12 (21.4%)	56 (100%)
> 20 Gy	1 (11.1%)	8 (88.9%)	9 (100%)
Total	45 (69.2%)	20 (30.8%)	65 (100%)

463 Chi-squared: 16.565

464 $p < 0.001$

465 Fisher's exact $p < 0.001$

466 **Table A4: Association Between Acute Pulmonary Toxicity and V20Gy > 30%**

V20	Toxicity No	Toxicity Yes	Row Total
< 30%	44 (88.0%)	6 (12.0%)	50 (100%)
> 30%	1 (6.7%)	14 (93.3%)	15 (100%)
Total	45 (69.2%)	20 (30.8%)	65 (100%)

467 Chi-squared: 35.832

468 $p < 0.001$

469 Fisher's exact $p < 0.001$

470 **Table A5: Association Between Acute Pulmonary Toxicity and V30Gy > 20%**

V30	Toxicity No	Toxicity Yes	Row Total
< 20%	40 (88.9%)	5 (11.1%)	45 (100%)
> 20%	5 (25.0%)	15 (75.0%)	20 (100%)
Total	45 (69.2%)	20 (30.8%)	65 (100%)

471   Chi-squared: 26.532

472   p < 0.001

473   Fisher's exact p < 0.001

474   **Annex A6:Kaplan-Meier Analysis of Overall Survival – Means, Medians, and**

475   **95% Confidence Intervals**

Means and medians for survival time

	Mean				Median	
			95 % confidence interval			
				Born		
Estimation	Error standard	Inferior born	superior	Estimation	Error standard
22,782	2,792	17,310	28,253	**16,000**	2,188

476

Means and medians for survival time

Median

95 % confidence interval

Inferior Born	Superior Born
11,711	20,289

477

478

Annex A7: Kaplan-Meier Analysis of Survival Based on GTV Volume – Means,

Medians, 95% Confidence Intervals and Log-rank Test Results for Survival

Differences by GTV Volume

Means and medians for survival time

	Mean				Median	
			95 % confidence interval			
GTV	Estimation	Error standard	Borne inférieure	Borne supérieure	Estimation	Error standard
0	**34,302**	7,136	20,315	48,289	**21,000**	5,028
1	**17,866**	2,220	13,516	22,217	**14,000**	3,412
Global	22,782	2,792	17,310	28,253	16,000	2,188

482

Means and medians for survival time

Median

95 % confidence interval

GTV	Inferior Born	Superior Born
0	11,146	30,854
1	7,312	20,688
Global	11,711	20,289

483

Global Comparaisons

	Khi-carré	ddl	Sig.
Log Rank (Mantel-Cox)	3,572	1	**,059**

484

485