Jana Publication & Research

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

VRC29

Document Details

Submission ID
trn:oid:::2945:313618894

Submission Date
Sep 20, 2025, 1:14 PM GMT+5:30

Download Date
Sep 20, 2025, 1:31 PM GMT+5:30

File Name
IJAR-53915.pdf

File Size
1.7 MB

30 Pages

5,474 Words

27,884 Characters

26% Overall Similarity

The combined total of all matches, including overlapping sources, for each database.

Filtered from the Report

- Bibliography
- Quoted Text

Match Groups

116 Not Cited or Quoted 25%
Matches with neither in-text citation nor quotation marks

5 Missing Quotations 1%
Matches that are still very similar to source material

0 Missing Citation 0%
Matches that have quotation marks, but no in-text citation

0 Cited and Quoted 0%
Matches with in-text citation present, but no quotation marks

Top Sources

19% Internet sources
23% Publications
10% Submitted works (Student Papers)

Match Groups

- 116 Not Cited or Quoted 25%
  Matches with neither in-text citation nor quotation marks
- 5 Missing Quotations 1%
  Matches that are still very similar to source material
- 0 Missing Citation 0%
  Matches that have quotation marks, but no in-text citation
- 0 Cited and Quoted 0%
  Matches with in-text citation present, but no quotation marks

Top Sources

- 19% Internet sources
- 23% Publications
- 10% Submitted works (Student Papers)

Top Sources

The sources with the highest number of matches within the submission. Overlapping sources will not be displayed.

1	Internet	link.springer.com 2%
2	Internet	www.researchgate.net 2%
3	Internet	www.science.gov 2%
4	Publication	"INVITED ABSTRACTS", Journal of Thoracic Oncology, 2013 2%
5	Publication	Tumors of the Chest, 2006. 1%
6	Internet	worldwidescience.org 1%
7	Internet	www.por-journal.com <1%
8	Publication	NA. "Supplement 2, Proceedings of the 14th World Conference on Lung Cancer, B... <1%
9	Internet	www.ncbi.nlm.nih.gov <1%
10	Internet	journal-api.s3.ap-south-1.amazonaws.com <1%

11	Internet	
jarem.org		<1%
12	Internet	
www.teorekol.lu.se		<1%
13	Internet	
www.frontiersin.org		<1%
14	Publication	
"Abstracts", Journal of Thoracic Oncology, 2009		<1%
15	Internet	
ww.thescipub.com		<1%
16	Internet	
pure.uva.nl		<1%
17	Internet	
jcancer.org		<1%
18	Publication	
Belderbos, J.S.A.. "Final results of a Phase I/II dose escalation trial in non-small-ce...		<1%
19	Publication	
Medical Radiology, 2014.		<1%
20	Internet	
coek.info		<1%
21	Internet	
bmcophthalmol.biomedcentral.com		<1%
22	Internet	
pmc.ncbi.nlm.nih.gov		<1%
23	Internet	
www.labome.org		<1%
24	Internet	
www.oncotarget.com		<1%

25 Publication
Akira Inoue, Hideo Kunitoh, Ikuo Sekine, Minako Sumi, Koichi Tokuuye, Nagahiro ... <1%

26 Publication
Shulian Wang. "Association between Systemic Chemotherapy before Chemoradia... <1%

27 Internet
ar.iiarjournals.org <1%

28 Publication
Medical Radiology, 2011. <1%

29 Student papers
Vrije Universiteit Amsterdam on 2024-11-27 <1%

30 Publication
Maria Luisa Veronese, Kenneth Algazy, Lisa Bearn, Beth Eaby, Jane Alavi, Tracey E... <1%

31 Internet
appliedradiationoncology.com <1%

32 Internet
wrap.warwick.ac.uk <1%

33 Internet
www.zlfzyj.com <1%

34 Publication
Tiziana Rancati, Claudio Fiorino. "Modelling Radiotherapy Side Effects - Practical ... <1%

35 Internet
aorticconference.org <1%

36 Publication
de Carvalho, Bruno Miguel Fernandes. "Characterization of Angiogenesis - Relate... <1%

37 Internet
dspace.univ-constantine3.dz <1%

38 Internet
www.eviq.org.au <1%

39 Internet

www.omicsdi.org <1%

40 Publication

George Rodrigues, Michael Lock, David D'Souza, Edward Yu, Jake Van Dyk. "Predic... <1%

41 Publication

Jeffrey D Bradley, Sasha Wahab, Mary Ann Lockett, Carlos A Perez, James A Purdy.... <1%

42 Publication

Kaynar, H.. "Clinical value of detection of metastasis of carina in patients with n... <1%

43 Student papers

KoN on 2025-07-21 <1%

44 Publication

Malignant Tumors of the Lung, 2004. <1%

45 Publication

Neha P. Amin. "Impact of Induction Chemotherapy on Estimated Risk of Radiatio... <1%

46 Publication

Singla, R.. "Simultaneous-integrated boost intensity-modulated radiation therapy... <1%

47 Student papers

Universitat Politècnica de València on 2020-05-22 <1%

48 Internet

cris.maastrichtuniversity.nl <1%

49 Internet

effiloop.com <1%

50 Internet

journals.plos.org <1%

51 Internet

library.unisel.edu.my <1%

52 Internet

www.roclv.com <1%

53 Internet

www.spandidos-publications.com <1%

54 Publication

"Abstracts", Journal of Thoracic Oncology, 2011 <1%

55 Publication

David A. Walker, Giorgio Perilongo, Roger E. Taylor, Ian F. Pollack. "Brain and Spin... <1%

56 Publication

Li-Jen Hsin, Tuan-Jen Fang, Ngan-Ming Tsang, Shy-Chyi Chin, Tzu-Chen Yen, Hsueh... <1%

57 Publication

Whitfield, Gillian Anne. "Development of Tools and Methodology for Image Guide... <1%

58 Publication

Xiao-Jing Zhang, Jian-Guo Sun, Jie Sun, Hua Ming, Xin-Xin Wang, Lei Wu, Zheng-Ta... <1%

59 Publication

Yun Oh. "Number of metastatic sites is a strong predictor of survival in patients ... <1%

60 Internet

ro-journal.biomedcentral.com <1%

61 Publication

Daly, Patricia E, and DL Ball. "Tumor size and outcomes in non-small-cell lung carc... <1%

62 Publication

Principles and Practice of Radiotherapy Techniques in Thoracic Malignancies, 2016. <1%

63 Publication

Tae Ryool Koo, Sung Ho Moon, Yu Jin Lim, Ja Young Kim et al. "The effect of tumor... <1%

64 Student papers

uva on 2019-11-16 <1%

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 ≥ 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).

Conclusion: Smaller GTV volumes were associated with improved survival. Dosimetric parameters were predictive of pulmonary toxicity, highlighting the importance of individualized treatment planning.

Keywords: Gross tumor volume, NSCLC, radiotherapy, survival, pulmonary toxicity, dosimetric parameters.

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.

Regarding radiation dose, larger tumor volumes typically receive lower doses to minimize toxicity, and chemoradiotherapy has been associated with increased lung and esophageal toxicity compared to radiation alone. Parameters derived from dose-volume histograms (DVH) are being studied for their role in lung toxicity development (1).

This study aims to assess whether GTV volume can predict survival outcomes and whether dosimetric factors correlate with the risk of acute pulmonary toxicity in patients with inoperable NSCLC undergoing 3D-CRT.

Materials and Methods

Design of Study and Eligibility: This retrospective, analytical, monocentric study was conducted at the Radiotherapy Department of CHU HASSAN II, Fez. It was approved by the Ethics Committee of the Hassan II University Hospital in Fez. Informed consent was obtained from all participants involved in the study. All patient data were anonymized to ensure confidentiality and privacy.

The clinical and dosimetric records of patients with non-small-cell lung cancer (NSCLC) were reviewed. Between January 2012 and July 2022, 65 patients treated with three-dimensional conformal radiotherapy (3D-CRT) for locally advanced NSCLC with curative intent were retrospectively analyzed. All patients had biopsy-proven NSCLC. Only patients with complete and exploitable clinical and dosimetric records were included in the study.

Patients were eligible if they had a confirmed diagnosis of NSCLC through biopsy and received 3D-CRT with curative intent. Only those followed up at the Radiotherapy Department of CHU HASSAN II, Fez, with complete and usable

records, were included in the study. Patients were excluded if they were treated with palliative intent, had incomplete or non-exploitable records, or were treated outside CHU HASSAN II, Fez.

Data Collection: Data were collected using a pre-established exploitation form based on medical records from the hospital network database, Hosixnet, as well as the ARIA Treatment Planning System (TPS).

Gross tumor volume (GTV) : The gross tumor volume (GTV), or macroscopic tumor volume, was delineated according to ICRU reports 50 and 62, and determined through endoscopy and imaging techniques such as CT scan, MRI, or PET scan.

The primary tumor was contoured using pulmonary CT windows. Mediastinal adenopathies were contoured separately using mediastinal windows. GTV and PTV were determined using the dose-planning system based on the CT data set.

Dosimetric Parameters Analyzed: The dosimetric parameters analyzed included the GTV volume in cm^3, the Mean Lung Dose (MLD) in Gray, and the lung volume receiving 20 Gy (V20Gy) and 30 Gy (V30Gy).

Acute Pulmonary Toxicity: Acute pulmonary toxicity was assessed by the radiation oncologist during weekly follow-up consultations and up to three months after the end of treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

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%),

42 divided into stage IIA (n=4; 6.15%) and stage IIB (n=7; 10.77%). The majority were diagnosed at stage III (n=53; 81.53%), subdivided into stage IIIA (n=16; 30.18%), IIIB (n=29; 54.71%) and IIIC (n=8; 15.09%).

129 **Table 1: Patient demographics and tumor characteristics**

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/m^2 on days 1 and 8, along with vinorelbine at 15 mg/m^2 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/m^2 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: OCisplatin + vinorelbine	66,66%
OCarboplatin + Paclitaxel	18,84%

152

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).

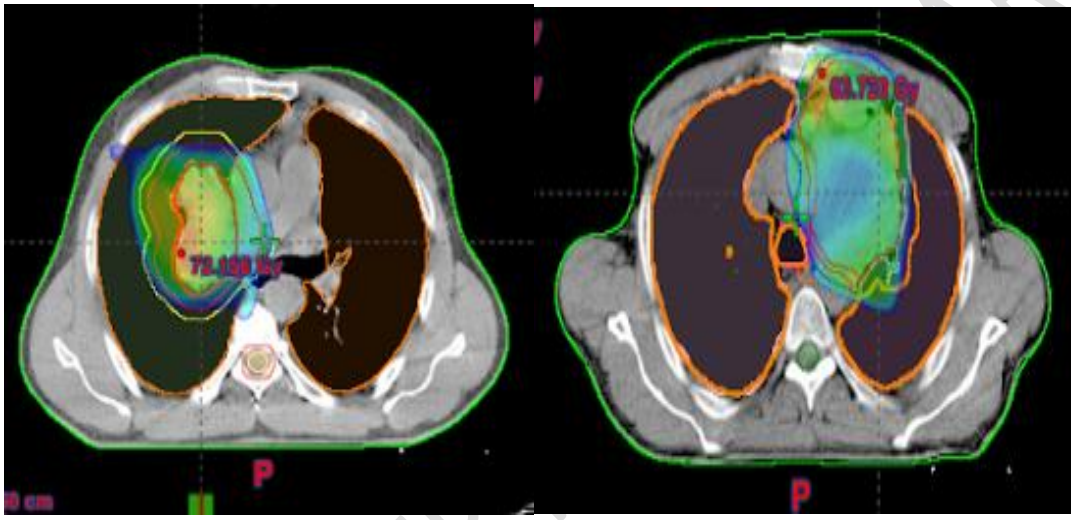
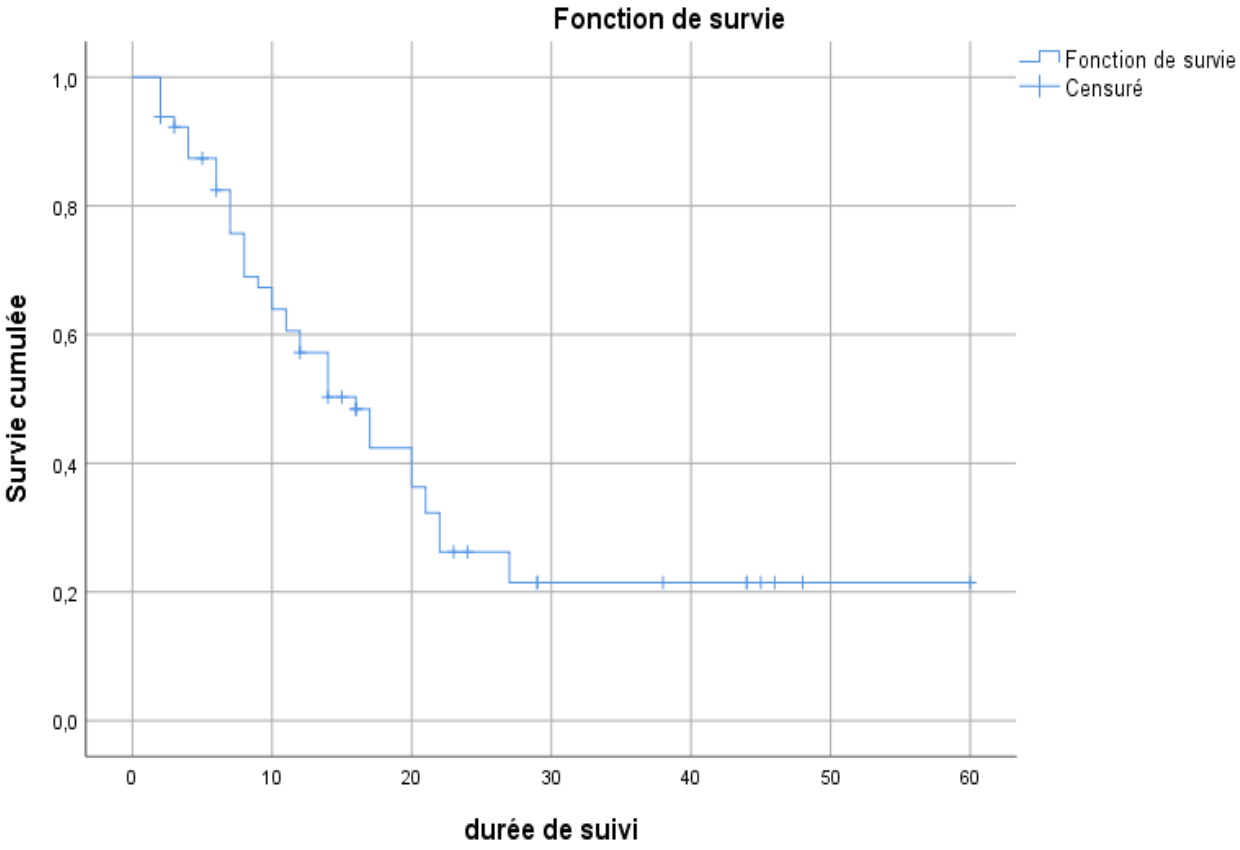


Figure.1 Example of intra-stage variation in GTV for two stage III patients (T4N0: 134 cm^3 vs T4N2: 416 cm^3).

4. Overall Survival Based on GTV Volume

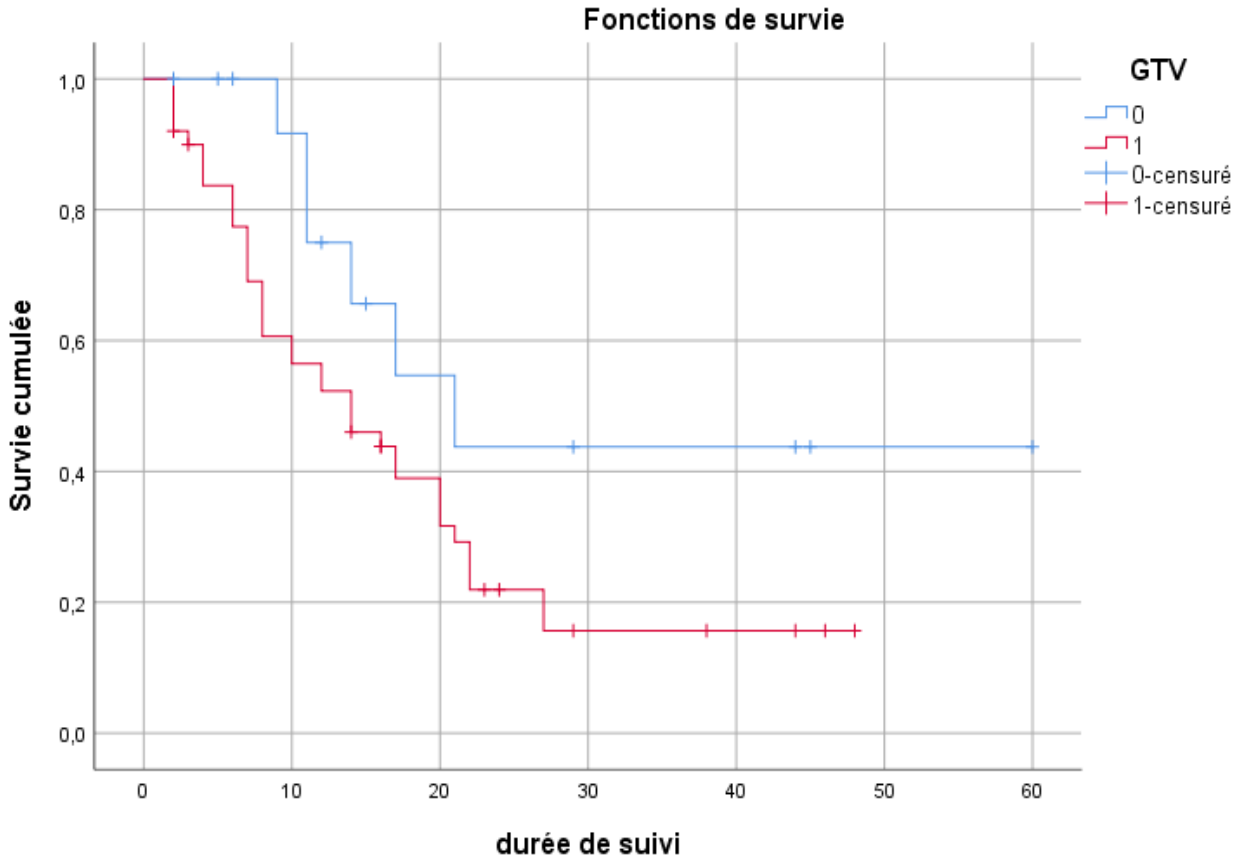
The mean overall survival for the cohort was 22.78 months (95% CI: 17.31–28.25 months)(**Figure 2, Annex A6)**.



164

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

38 166 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
24 168 with GTV volume ≥ 100 cc (Figure 2).
169 Although the difference did not reach statistical significance (Log-rank test, p =
36 170 0.059), there was a trend toward improved survival in patients with smaller
171 tumor volumes (**Figure 3**).



172

173 **Figure.3Overall survival according to GTV volume (cm^3) assessed by the**

174 **log-rank test.**

175 Detailed descriptive statistics including means, medians, standard errors,95%

176 confidence intervals for survival times and the global comparison of survival

177 curves by Log-rank test are summarized in **Annex A7**.

178 **5. Acute Pulmonary Toxicity and Dosimetric Parameters**

179 Acute pulmonary toxicity was observed in 20 out of 65 patients (30.76%). The

180 clinical presentation consisted of dry cough in 55% of cases (n=11) and dyspnea

181 in 45% (n=9).

Regarding the dosimetric parameters, the mean Mean Lung Dose (MLD) was 14.32 Gy (range: 2.7 to 33 Gy). The average lung volume receiving at least 20 Gy (V20Gy) and 30 Gy (V30Gy) was 17.52% (range: 3.4-46.3%) and 23% (range: 3-39%), respectively.

We performed Chi-squared tests to assess the association between acute pulmonary toxicity and several clinical and dosimetric parameters. The results are summarized in Annexes A1 to A5.

1. Age ≥60 years

There was no statistically significant association between age and acute pulmonary toxicity. Among patients aged under 60 years, 32% developed toxicity, compared to 30% in those aged ≥60 years ($p = 0.865$).

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

2. GTV Volume >100 cc

The analysis showed no significant relationship between GTV volume and acute pulmonary toxicity ($p = 0.377$). However, the toxicity rate appeared slightly higher in patients with GTV <100 cc (40%) compared to those with GTV >100 cc (28%).

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

3. Mean Lung Dose (MLD) >20 Gy

A statistically significant association was observed between MLD >20 Gy and acute pulmonary toxicity ($p < 0.001$). Among patients with MLD >20 Gy, 88.9%

experienced acute toxicity, versus only 21.4% in those with MLD <20 Gy. (See **Annex A3**, Table A3)

4. V20Gy >30%

There was a strong and statistically significant correlation between V20Gy >30% and acute pulmonary toxicity ($p < 0.001$). Toxicity was reported in 93.3% of patients with V20Gy >30%, compared to 12% for those below this threshold. (See **Annex A4**, Table A4)

5. V30Gy >20%

Similarly, a significant correlation was found between V30Gy >20% and toxicity ($p < 0.001$). Among patients with V30Gy >20%, 75% developed acute toxicity, compared to only 11.1% when V30Gy was <20%. (See **Annex A5**, Table A5)

These findings support the predictive value of certain dosimetric parameters (MLD, V20Gy, V30Gy) for pulmonary toxicity, while demographic and volumetric factors (age, GTV) did not reach statistical significance.

Discussion

Chemoradiotherapy, whether concurrent or sequential, is regarded as the standard first-line treatment for locally advanced nonresectable NSCLC patients with good performance status (10). However, the TNM staging system alone is not sufficient to predict the outcomes of radiotherapy or chemoradiotherapy in such cases (1–4). While tumor volume has been widely shown to have a stronger

correlation with survival and clinical outcomes than TNM stage in this context, appropriate prognostic cut-offs have yet to be established.

Our data indicate that a high pre-RT gross tumor volume (GTV) is associated with inferior overall survival (OS). This aligns with large datasets evaluating pre-treatment GTV and its impact on outcomes after RT, such as the study by Bradley et al. (3), who reported a strong influence of baseline GTV before RT on OS, cause-specific survival, and tumor control. They made a very accurate stratification, identifying five prognostic classes based on GTV among 207 stage I-IIIB NSCLC patients treated with definitive RT: GTV <25 cm^3, 25-60 cm^3, 60-110 cm^3, 110-180 cm^3, and >180 cm^3. Ninety-five patients with stage III disease received chemotherapy, but further stratification by GTV in this subgroup was not reported.

Similarly, Etiz et al. (4) found that among 150 patients treated with RT, GTV (<80 cm^3) was the most powerful independent predictor of survival, while N-stage (N0 vs N1-3) was only associated with time to progression (TTP). Even in the 111 patients with stage III disease in this study, GTV was the best predictor of survival.

Martel et al. (2) identified GTV (<200 cm^3) as a predictor of survival among 76 patients with stage I-IIIB disease, though the cut-off rationale was not described, and GTV lost significance in multivariate analysis when stage IIIB, nodal involvement, and age >65 years were considered.

Willner et al. (5) examined 135 patients at any stage (I–IV) and found GTV was significantly related to survival when stratified into three classes: <100 cm^3, 100-200 cm^3, and >200 cm^3. Finally, Werner-Wasik et al. (11) found that a GTV <63 cm^3 was a predictor of OS in 22 patients, most with stage III disease receiving chemotherapy in addition to thoracic RT.

A recent study by Xiaxia Chen et al. (2024) investigated the impact of GTV volume on the survival of patients with stage IV non-small cell lung cancer (NSCLC) treated with three-dimensional (3D) radiotherapy. The results showed that patients with a GTV of less than 150 cm^3 had significantly longer survival compared to those with a GTV greater than 150 cm^3. Multivariate analysis identified favorable prognostic factors, including peripheral lung cancer, a radiation dose of ≥63 Gy, and 4 to 6 cycles of chemotherapy.

The study further demonstrated that with 2 to 3 cycles of chemotherapy concurrent with 3D radiotherapy, patients with a GTV <150 cm^3 experienced better survival outcomes compared to those with a GTV ≥150 cm^3 ($p<0.05$). These findings underscore the importance of considering tumor volume in treatment planning to improve survival in stage IV NSCLC patients (**12**).

Our study also confirmed the importanceof GTV volume in predicting survival outcomes. The mean GTV in our cohort was 258 cm^3, with extremes ranging from 6.6 to 899 cm^3. Interestingly, we observed significant variations in tumor volumes even among patients with the same clinical stage. For instance, one patient with a T4N0 tumor had a GTV of 134 cm^3, while another with a T4N2

tumor had a GTV of 416 cm^3, as shown in Figure 1. This highlights the variability in tumor burden even within the same stage and emphasizes the need for precise volume-based stratification to guide treatment decisions.

Regarding toxicity, multivariate analyses in various studies have identified numerous variables directly related to the development of moderate to severe radiation pneumonitis (RP). These include patient characteristics, such as performance status (PS), female gender, pre-treatment FEV1, PaO2 less than 80 mmHg (13), or ongoing tobacco use as a protective factor (5); the type and schedule of concurrent chemotherapy (14–16); dose-volume histogram (DVH) parameters such as mean lung dose (MLD) (2.17.18), V20Gy (16.19.20), or V30Gy (21); radiation field size in series not using 3D RT (13); and theoretical models like normal tissue complication probability (NTCP) (2.17.18. 21 .22).

In all series, the addition of chemotherapy to radiation, particularly in the concurrent setting, seems to increase the risk of developing RP.

However, variability in toxicity grading systems (e.g., SWOG, RTOG, CTCAE) and in lung volume analysis methods may influence reported RP incidence (16.17.19).

In our study, we scored RP according to the 4th version of the CTCAE, which covers a wide range of pulmonary toxicities, including specific categories for radiation pneumonitis and other pulmonary complications. We also analyzed lungs as two separate organs, optimizing dose distribution, minimizing

complications, and improving outcomes based on individual lung characteristics and tumor location.

In our study, acute pulmonary toxicity was observed in 30.76% of patients, with dry cough and dyspnea being the most common symptoms. Regarding dosimetric parameters, we found that the mean lung dose (MLD) was 14.32 Gy (range: 2.7-33 Gy). Additionally, the volume of lung receiving 20 Gy (V20Gy) and 30 Gy (V30Gy) had a significant correlation with toxicity. Specifically, the mean volume of lung receiving 20 Gy (V20Gy) was 17.52% (range: 3.4-46.3%), and for V30Gy, it was 23% (range: 3-39%). These findings underline the importance of considering these dosimetric factors when planning treatment, as they correlate strongly with the development of pulmonary toxicity.

A meta-analysis by Roach et al. (23) on over 1900 patients undergoing chemoradiation therapy for NSCLC and SCLC identified total radiation dose >55 Gy and daily dose per fraction >2.67 Gy as key risk factors for RP. As total radiation dose correlates with survival and clinical outcome, efforts have been made to define the optimal dose considering higher toxicity with combined treatment compared to radiation or chemotherapy alone, especially concerning lung toxicity.

The advent of 3D-CRT has allowed the evaluation and correlation of numerous variables with toxicity to help radiation oncologists prevent this dose-limiting complication.

In our study, all evaluated DVH parameters, including MLD, V20Gy, and V30Gy, were independent predictors of developing radiation pneumonitis, which aligns with previous literature.

In addition to the findings from our study, a retrospective study by Nai-bin Chen et al. (24) (Radiation Oncology, 2020) aimed to develop and validate a new stratification system incorporating GTV-TNM for locally advanced non-small-cell lung cancer (NSCLC) treated with definitive 3D-conformal radiotherapy. The study included 340 patients, stratified into three groups based on GTV: G1 (<70 cm^3), G2 (70-180 cm^3), and G3 (>180 cm^3), as well as by TNM stage. The study demonstrated that a lower GTV-TNM group was associated with better overall survival and progression-free survival (P<0.001). The prognostic value of this GTV-TNM stratification system was validated by significant improvements in AUC scores (0.636 vs. 0.570, P=0.027) and F1 scores (0.655 vs. 0.615, p<0.001). This supports our findings that GTV volume plays a crucial role in survival outcomes in locally advanced NSCLC.

Furthermore, treatment strategies for locally advanced, inoperable non-small cell lung cancer (NSCLC) have seen rapid advancements in recent years. In the management of unresectable stage III NSCLC, the combination of chemotherapy and immunotherapy has shown a synergistic effect, improving both local and distant tumor control. Current guidelines for unresectable stage III NSCLC recommend chemotherapy followed by one year of immune checkpoint inhibitor (ICI) consolidation therapy.

However, several challenges remain, and further research is needed to determine the optimal timing for chemotherapy, radiation, and ICI administration, as well as the role of targeted therapies. A significant clinical hurdle in enhancing patient outcomes for advanced lung cancer is the development of resistance to immune checkpoint inhibitors (25).

Our retrospective analysis excluded adjuvant PD-L1 immunotherapy with durvalumab in stage III NSCLC post-chemoradiotherapy due to its unavailability during the study period, precluding conclusions on the interaction between GTV volume, survival, dosimetric parameters, and pulmonary toxicity during radiotherapy and adjuvant immunotherapy.

Nonetheless, this study highlights the critical importance of GTV volume and dosimetric parameters in predicting survival and the risk of radiation-induced pulmonary toxicity, offering valuable insights for clinical practice in NSCLC management.

Further prospective studies with larger sample sizes are needed to confirm these results and refine predictive models for acute pulmonary toxicity and survival outcomes.

Conclusion

This retrospective study highlights the association between pre-treatment GTV volume and overall survival (OS) in non-small-cell lung cancer (NSCLC) patients treated with three-dimensional conformal radiotherapy (3D-CRT). Patients with smaller GTV volume (<100 cm^3) had better survival outcomes. Additionally,

acute pulmonary toxicity was significantly associated with dosimetric parameters such as mean lung dose (MLD), V20Gy, and V30Gy, while no correlation was found with GTV volume or patient age.

These findings reinforce the importance of considering GTV volume and dosimetric parameters in treatment planning to optimize survival and minimize lung toxicity.

Furthermore, it may be valuable to integrate GTV volume into the TNM staging system to improve prognostic accuracy and guide treatment decisions. Future studies should further explore the impact of combination therapeutic approaches, including immunotherapy, on these factors.

References

1. Luigi De Petris; Ingmar Lax; Florin Sirzén; Signe Friesland. (2005). *Role of gross tumor volume on outcome and of dose parameters on toxicity of patients undergoing chemoradiotherapy for locally advanced non-small cell lung cancer. , 22(4), 375–381.* doi:10.1385/mo:22:4:375
2. Martel MK, et al. Volume and dose parameters for survival of nonsmall cell lung cancer patients. Radiother Oncol 1997;44:23–29.
3. Bradley JD, et al. Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 2002;52:49–57.
4. Etiz D, et al. Influence of tumor volume on survival in patients irradiated for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2002;53:835–846.
5. Willner J, Baier K, Caragiani E, Tschammler A, Flentje M. Dose, volume, and tumor control prediction in primary radiotherapy of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2002;52:382-389.
6. Basaki K, Abe Y, Aoki M, Kondo H, Hatayama Y, Nakaji S. Prognostic factors for survival in stage III non-small-cell lung cancer treated with definitive radiation therapy: impact of tumor volume. Int J Radiat Oncol Biol Phys. 2006;64:449-454.
7. Dubben HH, Thames HD, Beck-Bornholdt HP. Tumor volume: a basic and specific response predictor in radiotherapy. Radiother Oncol. 1998;47:167-174.

8. Ouyang WW, Su SF, Hu YX, et al. Radiation dose and survival of patients with stage IV non-small cell lung cancer undergoing concurrent chemotherapy and thoracic three-dimensional radiotherapy: reanalysis of the findings of a single-center prospective study. BMC Cancer. 2014;14:491.

9. Chen X, Zhang W, Luo L, Fu S, Cao D, Su S, Li Q, Yang W, Geng Y, Lu B, Ouyang W. Effect of primary tumor volume on survival of concurrent chemoradiotherapy in stage IV non-small cell lung cancer. Cancer Med. 2024 Sep;13(17):e70221. doi: 10.1002/cam4.70221. PMID: 39279741; PMCID: PMC11403300.

10. Pfister DG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004;22:330–353.

11. Werner-Wasik M, Xiao Y, Pequignot E, Curran WJ, Hauck W. Assessment of lung cancer response after nonoperative therapy: tumor diameter, bidimensional product, and volume. A serial CT scan-based study. Int J Radiat Oncol Biol Phys 2001;51:56–61.

12. Inoue A, et al. Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the longterm prognosis. Int J Radiat Oncol Biol Phys 2001;49: 649–655.

13. Yamada M, Kudoh S, Hirata K, Nakajima T, Yoshikawa J. Risk factors of pneumonitis following chemoradiotherapy for lung cancer. Eur J Cancer 1998;34:71–75.

14. Segawa Y, et al. Risk factors for development of radiation pneumonitis following radiation therapy with or without chemotherapy for lung cancer. Int J Radiat Oncol Biol Phys 1997;39:91–98.

15. Tsujino K, et al. Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2003;55:110–115.

16. Kwa SL, et al. Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 1998;42:1–9

17. Yorke ED, et al. Dose-volume factors contributing to the incidence of radiation pneumonitis in non-small-cell lung cancer patients treated with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 2002;54: 329–339.

18. Chen X, Zhang W, Luo L, et al. Effect of primary tumor volume on survival of concurrent chemoradiotherapy in stage IV non-small cell lung cancer. *Cancer Med*. 2024;13(17):e70221. doi:10.1002/cam4.70221.

19. Graham MV, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45: 323–329.

20. Jenkins P, D'Amico K, Benstead K, Elyan S. Radiation pneumonitis following treatment of non-small-cell lung cancer with continuous hyperfractionated accelerated radiotherapy (CHART). Int J Radiat Oncol Biol Phys 2003;56: 360–366.

433 **21.** Marks LB, et al. Physical and biological predictors of changes in whole-
434 lung function following thoracic irradiation. Int J Radiat Oncol Biol Phys
435 1997;39:563–570
436 **22.** Seppenwoolde Y, et al. Comparing different NTCP models that predict the
437 incidence of radiation pneumonitis. Normal tissue complication
438 probability. Int J Radiat Oncol Biol Phys 2003;55:724–735.
439 **23.** Roach M, 3rd, et al. Radiation pneumonitis following combined modality
440 therapy for lung cancer: analysis of prognostic factors. J Clin Oncol
441 1995;13:2606–2612.
442 **24.** Chen NB, Li QW, Zhu ZF, et al. Developing and validating an integrated
443 gross tumor volume (GTV)-TNM stratification system for supplementing
444 unresectable locally advanced non-small cell lung cancer treated with
445 concurrent chemoradiotherapy. *Radiat Oncol*. 2020;15(1):260. Published
446 2020 Nov 10. doi:10.1186/s13014-020-01704-2
447 **25.** Orosz Z, Kovács Á. The role of chemoradiotherapy and immunotherapy in
448 stage III NSCLC. Pathol Oncol Res. 2024 Apr 19;30:1611716. doi:
449 10.3389/pore.2024.1611716. PMID: 38706775; PMCID: PMC11066192.

450

Annexes

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%)

Chi-squared: 0.780

p = 0.377

Fisher's exact p = 0.524

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%)

Chi-squared: 0.029

p = 0.865

Fisher's exact p = 1.000

Table A3: Association Between Acute Pulmonary Toxicity and Mean Lung 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%)

Chi-squared: 16.565

$p < 0.001$

Fisher's exact $p < 0.001$

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%)

Chi-squared: 35.832

$p < 0.001$

Fisher's exact $p < 0.001$

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%)

Chi-squared: 26.532

$p < 0.001$

Fisher's exact $p < 0.001$

Annex A6:Kaplan-Meier Analysis of Overall Survival – Means, Medians, and 95% Confidence Intervals

Means and medians for survival time

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

Means and medians for survival time

Median	
95 % confidence interval	
Inferior Born	Superior Born
11,711	20,289

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

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

Global Comparaisons

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