



Toxicity after volumetric modulated arc therapy for lung cancer: a monocentric retrospective study

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Background: Intensity-modulated radiotherapy (RT) is now widely implemented and has replaced classical three-dimensional (3D)-RT in many tumor sites, as it allows a better target dose conformity and a better sparing of organs at risk (OAR), at the expense, however, of increasing the volume of low dose to normal tissues. Clinical data on toxicities using volumetric modulated arc therapy (VMAT) in lung cancer remain scarce. We aimed to report both acute (APT) and late (LPT) pulmonary and acute (AET) and late (LET) oesophageal toxicities in such setting.

Methods: All patients treated for a primary lung cancer with VMAT +/- chemotherapy (ChT) in our center from 2014 to 2018 were retrospectively included. Usual clinical, treatment and dosimetric features were collected. Univariate analysis was performed using the receiver operative characteristics approach while multivariate analysis (MVA) relied on logistic regression, calculated with Medcalc 14.8.1.

Results: In total, 167 patients were included, with a median age of 66 years (39–88 years). Median radiation dose was 66 Gy (30–66 Gy); 82% patients received concomitant (32.3%), induction (25.7%) or induction followed by concomitant ChT (24%). After a median follow-up of 14.0 months, the G ≥ 2 APT, AET, LPT and LET rates were 22.2%, 30.0%, 16.8% and 5.4%, respectively with low grade ≥ 3 toxicity rates (respectively, 3%, 6.6%, 3% and 0%). On MVA, APT was significantly associated with V30 to the homolateral lung, AET with age, LPT with MEVS while no feature remained significantly correlated with LET.

Conclusions: Low rates of pulmonary and esophageal toxicity were observed in our cohort. Larger prospective studies are needed to confirm these results.

Keywords: Volumetric modulated arc therapy (VMAT); pulmonary toxicity; lung toxicity; lung cancer

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Introduction

With 228,150 new cases expected for 2019, lung cancer is the leading cancer killer in the United States (1). Concomitant chemoradiotherapy (cChRT) is the standard of care for locally-advanced lung cancer (2), but the addition of chemotherapy (ChT) to radiotherapy (RT) is known to

increase acute toxicity. Indeed, in the study of Parashar and al, the incidence of grade 2 or higher radiation pneumonitis was significantly associated with the addition of ChT (62.7% versus 15.8%, $P < 0.001$) in patients treated with three-dimensional conformal (3D)-RT (3). While metastasis-free survival and overall survival (OS) were significantly improved with the addition of durvalumab (4,5), acute and

late toxicities remain one of the main concerns in patients treated with RT for localized lung cancers.

Intensity-modulated RT (IMRT) is now widely implemented and has replaced classical RT (3D-RT) in many tumor sites, as it allows a better target dose conformity and a better sparing of organs at risk (OAR) without compromising tumor control (6-8). This higher conformation using IMRT is possible at the expense of a volume increase in adjacent organs receiving doses in the lowest range. This “low-dose bath” may theoretically increase toxicity in the adjacent healthy tissues, especially in the lungs, despite being not really clinically reported (9-11). In a retrospective cohort of 73 patients treated with hypofractionated IMRT (2.2–2.75 Gy/fraction), severe pneumonitis and esophagitis (grade ≥ 3) occurred in only 7% and 1% of the population, respectively (12). For volumetric modulated arc therapy (VMAT), this low dose bath, reflected by the V5% to the lungs, has raised even more concerns. In addition to the higher theoretical risk of developing secondary malignancy (13,14), the rate of radiological pneumonitis may be higher in patients treated with VMAT compared with conformal 3D-RT (15,16). However, reported results are contradictory in terms of occurrence of lung complications following IMRT or VMAT (17,18).

Published clinical data on outcome and toxicity using VMAT in lung cancer outside clinical trial are still scarce, especially in patients receiving concomitant ChT. We aimed to report acute and late pulmonary and oesophageal toxicities in a cohort of patients with lung cancer and treated with VMAT with or without ChT at our institution.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-406>).

Methods

Patients and treatment characteristics

All consecutive patients treated with (chemo-)RT using VMAT delivered with curative intent for lung cancer between November 2015 and January 2018 at the University Hospital of Brest were included. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the CHRU Brest Hospital (IRB 29BRC20.0154). All patients consented for the use of their clinical data for scientific purpose.

Prior to treatment initiation, patients underwent a total body ^{18}F -fluorodeoxyglucose positron emission tomography combined with low dose computed tomography (^{18}F FDG PET-CT) and magnetic resonance imaging (MRI) or CT-scan of the brain for tumour staging purposes. All patients had pulmonary function tests before RT initiation. Patients in good clinical condition (performance status of 0 to 1) received cChRT. Patients with impaired performance status (i.e., ≥ 2) underwent RT alone. When bulky masses were present and considered as non-eligible to upfront irradiation, induction ChT was the treatment of choice, followed by cChRT. In case of persistent toxicity after induction ChT, RT alone was administered. RT was delivered using VMAT on a Truebeam Novalis STX (RapidArc[®], Varian, United States) using two arcs of 6 MegaVolt.

Treatment planning

All patients had a PET/CT for the RT planning. Planning CT consisted of an intravenous contrast-enhanced CT scan in treatment position acquired from the third cervical vertebral to the upper abdomen (including a slow CT-scan of the primary tumour) which was then transferred to the Pinnacle planning system (Version 9.10; Philips Radiation Oncology Systems, Fitchburg, WI).

The gross tumour volume (GTV) consisted of the primary tumour and metastatic lymph nodes (confirmed by histopathological examination and/or FDG-PET positive) outlined on the planning CT after registration with the diagnostic FDG-PET. The clinical target volume (CTV) enclosed the GTV of the primary tumour (19) and positive lymph nodes (20) with margins defined by the Radiation Therapy Oncology Group (RTOG) recommendations depending on the histology (20-22). Planning target volumes (PTVs) were created by an isotropic 5 mm expansion of the CTVs. To generate dose-volume histogram (DVH) data, the lungs and the oesophagus (from the lower border of the cricoid cartilage to the gastro-oesophageal junction) were manually delineated. The spinal cord was considered to be at the inner margin of the entire bony thoracic spinal canal.

The prescribed dose to the PTV was 66 Gy in 33 daily fractions, 60 Gy in 30 fractions in case of small cell lung cancer, or less depending on the treatment planning and dose to organs at risk. Usual dose constraints were considered: V30Gy <20%, V20Gy <30%, V13Gy <40%, V10Gy <45%, and V5Gy <65% for the lungs (23), V40Gy to the heart

<30% (24) and V60Gy to the esophagus <33% (25), VxGy being the percentage of the organ receiving x Gy.

Assessment of toxicity and therapeutic outcome

During the course of radiation delivery, acute esophageal toxicity (AET) and pulmonary toxicity (APT) were assessed weekly by the treating radiation oncologist using the Common Terminology Criteria for Adverse Events (CTCAE) v.4. Follow-up visits were planned at one month and every three months thereafter for the first two years. Thoraco-abdominal-pelvic CT-scan was performed at one month following RT completion and every three months for two years thereafter. Late pulmonary and esophageal toxicities (LPT and LET, respectively) were also scored using the CTCAE v.4 from the fourth months following RT completion and every 3 months.

To distinguish ChT and RT toxicities, toxicities specifically due to ChT were also collected during and after the radiation delivery. Here, we only report toxicities due to RT. Indeed, the ChT toxicity profile is significantly different with, mainly and depending on the ChT regimen, systemic toxicities such as gastro-intestinal (nausea, ...), haematological (neutropenia, anemia, ...), renal and neurologic (neuropathy). In the cChRT setting, ChT is used as a radio-sensibilization agent. Therefore, toxicities are often due to the RT but increased by ChT.

Data collection and statistical analysis

All medical records were retrospectively reviewed. The following parameters were extracted from the treatment planning system: PTV volume; for the homolateral and contralateral lung mean lung dose (DMean), maximum dose (DMax), V5Gy, V10Gy, V13Gy, V20Gy, V30Gy; for both lungs: V13Gy, V20Gy, V30Gy, DMax and DMean; for the esophagus: V5Gy, V10Gy, V20Gy, V30Gy, V40Gy, V50Gy, V60Gy and maximum esophagus dose; for the heart: mean dose, V40Gy, V30Gy.

Association of clinical characteristics and dosimetric parameters with the occurrence of grade (G) ≥ 2 toxicity (AET, LET, APT and LPT) was evaluated with univariate analyses using the Receiver Operative Characteristics approach (area under the curve: AUC, sensitivity: Se, specificity: Sp), calculated with Medcalc 14.8.1. Multivariate analysis (MVA) using logistic regression was performed on pre-selected significant clinical and dosimetric features. A p-value below 0.05 indicated statistical significance.

All CT-scan during the follow-up were reviewed and the aspect compatible with radiation induced injuries were collected at 1, 3, 6, 9, and 12 months after RT, and described as “alveolar opacities”, “ground glass” and/or “fibrosis”. Then these radiation induced lung diseases (RILD) were noted according to their locations: around the tumour, in the same lobe as the tumour, in the same lung, in the contralateral lung or in both lungs. The impact of dosimetric and clinical parameters on the occurrence of RILD was also studied.

OS, progression-free-survival (PFS) and local control (LC) were also reported using the Kaplan Meier method.

Results

Population

One hundred and sixty-seven patients were included. Patients' characteristics are listed in *Table 1*. Median age was 66 years (range, 39–88 years). According to the American Joint Committee on Cancer (AJCC) 2017 classification 1.8% (n=3), 6.6% (n=11), 7.8% (n=13), 40.1% (n=67), 34.1% (n=57), 1.8% (n=3) and 7.8% (n=13) patients presented with a staged I, IIA, IIB, IIIA, IIIB, IIIC, and IV disease, respectively. Among them, 37.7% (n=63) had a squamous cell carcinoma, 40.1% (n=67) an adenocarcinoma, 14.4% (n=24) a small cell lung carcinoma and 7.8% (n=13) had other histologies.

Treatments characteristics

Median PTV volume was 270 cc (14.2–1,408 cc). Median radiation dose was 66 Gy (range, 30–66 Gy). The dose was reduced to 60 Gy in 60 patients either because of a small cell histology (n=24) or due to violation of normal tissue constraints (n=36). Three patients received less than 60 Gy due to major disease progression or death. Most patients (82%) received ChT. Many different regimens were used, depending on histology, patient's performance status and past history and comorbidities. Overall, 54 patients (32.3%) patients received cCRT, 43 (25.7%) had sequential RT, 40 (24.0%) were treated with induction ChT followed by cChRT and 30 (18.0%) had exclusive RT (*Table 1*).

Dosimetric parameters are summarised in *Table S1*. Median V20Gy and V30Gy to both lungs were 23.0% (18.3–28.0%) and 14.4% (9.7–18.3%), respectively. Median V60Gy to the oesophagus was 8.7% (5.4–11.3%) and median dose to the heart 8.5 Gy (0.11–30.5 Gy).

Table 1 Patients and disease characteristics

Characteristics	n=167	%
Age median (year)	66 [39–88]	
Gender		
Male	113	67.7
Female	54	32.3
Smoking		
Active	65	39
Former/never	102	61
Known COPD	63	37.7
Mean MEVS (%)	74 [23–122]	
Histology		
SCC	63	37.7
ADC	67	40.1
SCLC	24	14.4
Others	13	7.8
AJCC stage		
I	3	1.8
II A	11	6.6
II B	13	7.8
III A	67	40.1
III B	57	34.1
III C	3	1.8
IV	13	7.8
Total RT dose		
66 Gy	103	61.7
60 Gy	60	35.9
64 Gy	1	0.6
59.4 Gy*	1	0.6
58 Gy	1	0.6
30 Gy	1	0.6
Chemotherapy sequence		
Concomitant	54	32.3
Induction	43	25.7
Induction + concomitant	40	24.0
None	30	18.0

Table 1 (continued)

Table 1 (continued)

Characteristics	n=167	%
Chemotherapy regimen		
Carboplatin pemetrexed	9	5.4
Carboplatin vinorelbine	3	1.8
Carboplatin paclitaxel	27	16.2
CDDP pemetrexed	5	3.0
CDDP vinorelbine	58	34.7
Carboplatin or CDDP - VP16	24	14.4
Other	12	7.2
Adjuvant durvalumab	16	9.6

*, fractionation: 1.8 Gy by fraction. Otherwise, 2 Gy/fraction. COPD, chronic obstructive pulmonary disease; MEVS, maximum expiratory volume per second; PTV, planning target volume; CDDP, cisplatin; RT, radiotherapy; AJCC, American Joint Committee on Cancer; SCC, squamous cell carcinoma; ADC, adenocarcinoma; SCLC, small cell lung cancer.

Acute and late pulmonary and oesophageal toxicities

The G ≥2 APT, AET, LPT, and LET toxicity rates for the entire cohort were respectively 22.2%, 30.0%, 16.8% and 5.4%. Grade 3 and above APT, AET and LPT remained relatively rare with respective rates of 3%, 6.6% and 3%. No grade ≥3 LET occurred.

Esophageal toxicity

AET G ≥2 was observed in 5 (25%), 18 (33.3%), 16 (31.4%) and 11 (32.4%) patients after exclusive RT, cChRT, sequential RT and induction ChT followed by cChRT, respectively. On univariate analysis, only age, DMean, V30 and V60 to the esophagus with respective threshold of 27.5 Gy, 43% and 12.4% were significantly associated with a risk of AET >G2 (Table 2). On MVA, only age remained significant (P=0.03). Patients older than 67 years were twice more likely to present a grade ≥2 AET than younger patients, with respective rates of 42.3% and 20.9%.

Overall, occurrence of severe LET remained low: only 9 patients (5.4%) developed G ≥2 toxicity (respectively, 1, 5 and 3 the cCRT, sequential, and induction + cChRT groups). On univariate analysis, no clinical or dosimetric features achieved a significant correlation (Table 2).

Table 2 Grade ≥ 2 acute and late esophageal toxicity and correlations with clinical and dosimetric parameters in univariate and multivariate analysis

Feature	Acute esophageal toxicity						Late esophageal toxicity: univariate analysis			
	Univariate analysis				Multivariate analysis		AUC	Se	Sp	P
	AUC	Se	Sp	P	OR	P				
Clinical										
Age	0.61	60.0	65.0	0.03	1.05	0.009	0.52	44.4	72.2	0.82
Smoking	0.50	38.9	62.6	0.94			0.60	55.6	63.5	0.29
AJCC stage	0.52	46.0	56.9	0.70			0.60	100.0	16.6	0.21
RT dose	0.51	64.0	39.3	0.78			0.62	66.7	62.7	0.14
Chemotherapy sequence	0.53	90.0	17.1	0.53			0.55	88.9	35.4	0.49
Durvalumab	0.52	12.0	92.3	0.41			0.51	11.1	91.1	0.84
PTV volume	0.53	94.0	18.0	0.55			0.54	77.8	46.8	0.58
RT duration	0.56	68.0	47.0	0.19			0.63	88.9	38.0	0.11
Oesophagus dosimetric parameters										
DMean	0.62	46.0	75.2	0.02	1.10	0.15	0.51	100.0	21.0	0.96
DMax	0.57	86.0	31.6	0.14			0.52	77.8	39.2	0.80
V5	0.59	56.0	65.0	0.08			0.51	55.6	24.1	0.92
V10	0.57	64.0	57.3	0.15			0.50	0.00	77.9	0.98
V20	0.61	52.0	71.8	0.03	0.95	0.13	0.51	0.00	85.4	0.96
V30	0.61	52.0	71.8	0.03	1.03	0.53	0.52	88.9	29.1	0.82
V40	0.59	42.0	75.2	0.08			0.51	88.9	31.0	0.86
V50	0.58	72.0	47.9	0.10			0.55	88.9	36.1	0.55
V60	0.62	58.0	69.2	0.02	1.01	0.71	0.52	44.4	70.9	0.83

COPD, chronic obstructive pulmonary disease; MEVS, maximum expiratory volume per second; PS, performance status; RT, radiation therapy; VxGy, volume of the organ receiving xGy; DMean, mean dose to the oesophagus.

Pulmonary toxicity

The rates of APT did not significantly vary according to the modality of ChT administration. On univariate analysis (Table 3), PTV volume and V30 (with a cut off of 22.2 Gy) to the homolateral lung were significantly associated with increased G ≥ 2 APT. Only the V30 to the homolateral lung remained statistically correlated with G ≥ 2 APT on MVA (P=0.007). Patients with a V30 to the homolateral lung >22.2 Gy were 3 times more likely to present a grade ≥ 2 APT than patients with V30 below 22.2 Gy, with respective rates of 33.3% vs. 11%.

The rate of severe LPT was relatively low: 13.2% patients developed a grade 2 LPT, 2.4% a grade 3 and only 0.6% developed a grade 4 LPT. To be noted, one patient

died following treatment related pulmonary toxicity (grade 5 LPT) in the Induction-cChRT group. All > grade 2 LPT occurred in a ChT setting (1 G3 in the cChRT group, 2 G3 and 1 G4 in the sequential group and 2 G3 in the Induction-cChRT group).

On univariate analysis, only the pre-radiotherapy MEVS was associated with the occurrence of G ≥ 2 LPT. No association with ChT regimen nor dosimetric features was statistically relevant (Table 3).

RILD

Considering all types of RILD, the rates of contralateral radiological injuries observed on CT-scan were 5.4% at

Table 3 Grade ≥ 2 acute and late pulmonary toxicity and correlations with selected clinical and dosimetric parameters in univariate and multivariate analysis

Feature	Acute pulmonary toxicity						Late pulmonary toxicity					
	Univariate analysis				Multivariate analysis		Univariate analysis				Multivariate analysis	
	AUC	Se	Sp	P	OR	P	AUC	Se	Sp	P	OR	P
Clinical												
Age	0.56	84.2	32.6	0.27			0.55	89.3	33.1	0.33		
Smoking	0.53	42.1	63.8	0.52			0.51	39.3	62.8	0.84		
COPD	0.52	42.1	62.8	0.59			0.59	53.6	64.8	0.08		
MEVS	0.53	31.6	83.7	0.66			0.64	57.1	75.5	0.02	0.97	0.02
AJCC stage	0.53	52.6	58.6	0.59			0.55	39.3	89.1	0.15		
RT dose	0.57	50.0	65.1	0.15			0.51	0	97.8	0.91		
CT sequence	0.55	73.7	36.4	0.33			0.61	53.6	68.4	0.06		
Durvalumab	0.56	100.0	11.6	<0.0001	1.0	0.99	0.55	100.0	10.8	<0.0001	1.0	0.99
PTV volume	0.63	57.8	68.2	0.01	1.0	0.72	0.55	46.4	72.7	0.41		
RT duration	0.54	86.8	24.0	0.46			0.52	14.3	95.0	0.72		
Homolateral lung dosimetric parameters												
DMean	0.61	81.6	43.4	0.02	1.10	0.15	0.58	71.4	53.2	0.18		
DMax	0.50	23.7	89.2	0.98			0.57	42.9	74.1	0.27		
V5	0.56	34.2	80.6	0.24			0.57	46.4	71.2	0.23		
V10	0.58	73.7	41.1	0.15			0.55	42.9	71.2	0.45		
V13	0.58	76.3	39.5	0.15			0.55	35.7	79.9	0.41		
V20	0.62	78.9	48.8	0.01	1.03	0.60	0.56	39.3	76.3	0.32		
V30	0.64	79.0	51.2	0.005	1.10	0.007	0.58	60.7	56.1	0.21		
Contralateral lung dosimetric parameters												
DMean	0.52	24.4	83.6	0.71			0.56	60.7	54.0	0.32		
DMax	0.51	13.5	75.0	0.91			0.51	82.1	3.70	0.89		
V5	0.57	40.5	75.8	0.23			0.55	35.7	82.5	0.47		
V10	0.54	62.2	49.2	0.42			0.59	32.1	83.2	0.14		
V13	0.53	73.0	38.3	0.65			0.59	60.7	56.9	0.13		
V20	0.50	75.7	33.6	0.94			0.59	71.4	48.2	0.11		
V30	0.50	75.7	35.2	0.94			0.57	78.6	38.7	0.23		
Both lungs dosimetric parameters												
DMean	0.57	70.3	46.1	0.17			0.55	57.1	60.6	0.44		
V13	0.53	89.2	22.7	0.52			0.52	89.3	19.7	0.75		
V20	0.60	70.3	53.1	0.05			0.51	21.4	85.4	0.87		
V30	0.64	89.2	38.3	0.005	1.03	0.69	0.60	50.0	78.1	0.13		

COPD, chronic obstructive pulmonary disease; MEVS, maximum expiratory volume per second; PS, performance status; RT, radiation therapy; VxGy, volume of the organ receiving xGy; DMean, mean dose to the oesophagus; CT, chemotherapy.

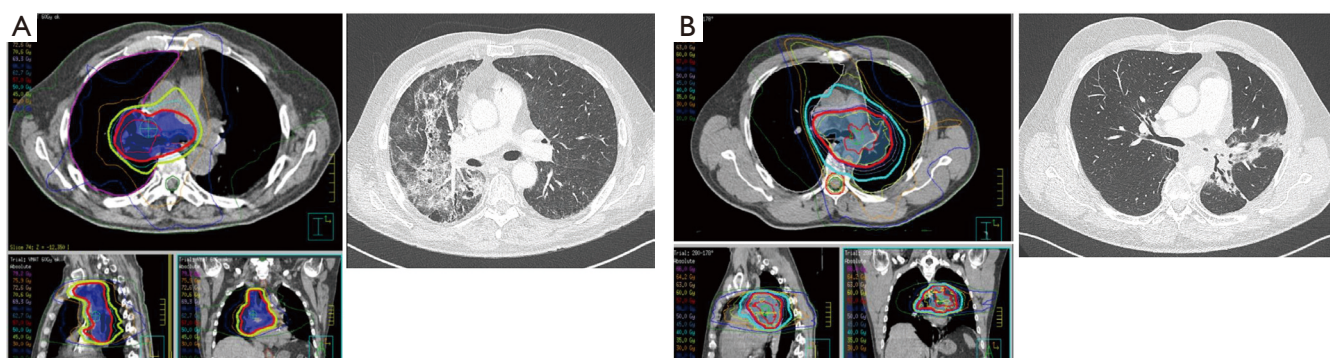


Figure 1 Dose distributions and radiation induced lung injury. (A) Example of dose distribution of a lung tumour located in middle lobe and paracardial segment of the right lower lobe, and corresponding CT-scan done 3 months after radiotherapy completion and showing a radiation induced lung injury with ground glass. (B) Example of dose distribution of a lung tumour located in the upper segment of the left lower lobe and corresponding CT-scan done at 12 months showing a radiation induced lung injury with fibrosis.

one month, 5.4% at 3 months and 1.0% at 1 year, while the rate of bilateral RILD were 9.0% and 3.2%, respectively. The RILD during the follow-up at 3 and 12 months are reported in [Table S2](#). *Figure 1* illustrates examples of RILD that occurred following VMAT and the corresponding dosimetry. Given the low number of events at 9 and 12 months, association of clinical and dosimetric factors with the occurrence of RILD was only tested at 3 and 6 months, and no correlation was found.

Treatment outcomes

Median follow-up was 14.0 months (range, 0.4–47.8). The 1-year LC was 83.3% for the entire cohort, with respective values of 91.2%, 85.2%, 76.1%, 71.8% in the cChRT, sequential, induction + cChRT and RT only groups. No statistically significant differences in LC between the groups were observed ([Figure S1](#)). Among the 167 patients, the 1-year PFS was 49.2% ([Figure S2](#)). At last follow-up, 60 patients had died, all due to disease. The 1-year OS was 70.7% ([Figure S3](#)). As expected, patients with a small cell histology had poorer PFS and OS outcomes.

Discussion

VMAT has the advantage of delivering the dose to the tumour in a 360 degrees rotation in less than two minutes. But, the increase in normal tissue volume receiving low dose radiation has raised some concern, supported by conflicting clinical results. While Mc Grath and colleagues showed that VMAT was better than 3D-RT at sparing lung (V20Gy,

V12.5Gy, V10Gy, V5Gy) compared with 3D-RT (26), opposite results have been published by Ong *et al.*, who found higher lung dosimetric parameters (V20Gy and V5Gy) with VMAT compared with 3D-RT (27). Toxicity outcomes following VMAT-based RT for lung cancer lack, thus our work.

With 22.8%, APT, 30.0% AET, 16.8% LPT and 5.4% LET, the grade ≥ 2 toxicity rates observed in our cohort are in line with previous published reports focusing on IMRT (9,18,28). Data from the RTOG 0617 study that compared the use of 3D-RT to IMRT in 482 patients showed indeed that IMRT was associated with fewer G3 pneumonitis compared to the 3D-RT technique (7.9% *vs.* 3.5%, $P=0.039$) and with a reduced risk of radiation pneumonitis in adjusted analyses (OR, 0.41; 95% CI, 0.17–0.99; $P=0.046$). Doses to the heart, especially the V40Gy was also lower using IMRT ($P<0.05$). On the contrary, the lung V5Gy was not correlated with any G3 toxicity (29). On the contrary, Ling *et al.* did not show any difference in terms of acute toxicity between IMRT and 3D-RT in a retrospective series of 145 patients, but there was a trend toward lower rates of G ≥ 2 pneumonitis among IMRT patients compared to 3D-RT patients (5.4% *vs.* 23.0%, $P=0.065$) (28).

Very few data on VMAT-related toxicity in patients treated for lung cancer are however currently available in the literature ([Table S3](#)). Based on a 77-patient cohort, Wu reported low grade ≥ 2 toxicities with respective rates of G ≥ 2 APT and AET of 28.6% and 18.2%. No data on late toxicities were however reported (30) and association between acute toxicities and clinical or dosimetric features was not tested.

The largest VMAT cohort (278 patients), focusing on lung toxicity only, accounted for a \geq G2 radiation pneumonitis rate of 7.6%. Unfortunately, the overall population's characteristics (PTV volume, AJCC stage, ...) being unavailable, comparison with our cohort is not possible (31).

Acute esophageal toxicity rates of IMRT in the literature seem to be higher than the ones we observed here with VMAT, with rates ranging between 45% and 72% (32-35). In a study comparing toxicity and outcome between IMRT and VMAT in 188 patients treated for advanced stage NSCLC, APT and severe late toxicities were however similar to ours: the rate of G2 APT (23.9%) in patients treated with IMRT was not significantly different from the rate reported in patients treated using VMAT (18.8%) (18). Compared to IMRT, the risk of developing a $G \geq 2$ AET after VMAT was also higher in this study, but the authors attributed it to the higher percentage of patients receiving cChRT in the VMAT group.

Concomitant ChT was not associated with a higher risk of toxicity in our study. cCRT is the standard of care in patients with NSCLC (33), but ChT is known to have a radiosensitizing effect resulting in enhanced mucosal toxicity when combined with RT (3,34,35). In a meta-analysis, Palma *et al.* found that age (>65) and administration of concomitant carboplatin/paclitaxel ChT were predictive factors for radiation induced lung toxicities (15). Similarly, in a cohort of lung cancer patients predominantly treated with concurrent carboplatin/paclitaxel, both cChRT use and age were associated with a large increase in acute lung toxicities risk (63% versus 16%), with a trend toward increased risk in patients receiving carboplatin/paclitaxel specifically. Pneumonitis occurred in 77% of patients aged 61–70, with lower rates in other patients (3). In our cohort, toxicity rates were significantly lower than the ones reported in patients treated with 3D-CRT, possibly thanks to the higher tumour-conformation and thus lower oesophagus and lungs dose profiles, erasing concomitant ChT as a potential toxicity factor. In total, one can think VMAT could enhance cChRT tolerance without compromising tumour control (6-8).

On MVA, adjuvant durvalumab was not correlated with any form of acute or late toxicities in our study. Adjuvant durvalumab has recently been shown to increase PFS and OS (4,5), but only a small subgroup of patients received durvalumab in our cohort (9.6 %). The rate of grade ≥ 2 AET in this sub-population (43.8%) was higher than in

the rest of the population (28.5%), despite not reaching statistical significance ($P=0.32$). Anti-PD-L1 related pneumonitis is now well described and occurs in around 5% of patients with anti-PDL1, as observed in the Keynote 024 (36). But, no data on AET are available in patients treated with durvalumab specifically.

As we experienced, differentiating expected RILD from recurrence, infection and others lung diseases is difficult (37). Radiation induced inflammatory events that occurred after radiation therapy are likely to result in scannographic modifications (38) but data are missing in the literature regarding the radiological semiology in this context. To our knowledge, no study has established a correlation between dosimetric parameters (especially low doses such as V5Gy, V10Gy, and V13Gy) and the radiological appearance of the lung parenchyma on CT-scan after radiation. But, the contralateral and bilateral injuries we observed here may be the direct reflection of this modern irradiation technique.

Besides the drawbacks of retrospective studies, some other limitations of our work should be noted. Firstly, no control group treated with 3D-RT or IMRT is available. Secondly, the present cohort is heterogeneous in terms of histology, RT dose, and ChT modality. Thirdly, the limited follow-up makes the interpretation of late toxicity rates difficult although we could argue that the aggressiveness and poor PFS of the disease makes long-term complications difficult to assess and that the majority of events usually occur during the first year after treatment (39).

Conclusions

The low rates of pulmonary and esophageal toxicity observed in our cohort of patients treated with arc therapy for lung cancer show that the use of arc therapy appears to be a safe irradiation technique. Larger prospective studies are needed, ideally with respiratory function tests during the follow-up, to analyse the clinical consequence of the VMAT technique on respiratory parameters. Such a study is currently ongoing at our institution (NCT03931356). Moreover, the radiological semiology of pneumonitis induced by immunotherapy and/or induced by VMAT also needs to be further studied.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tlcr-20-406>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the CHRU Brest Hospital (IRB 29BRC20.0154). All patients consented for the use of their clinical data for scientific purpose.

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Table S1 Dose-volume histogram parameters

DVH parameter	Homolateral lung	Contralateral lung	Bilateral lungs	Heart	Esophagus
V5Gy	61.8 (48.8–74.6)	51.6 (42–64.9)	58.2 (47.1–69.1)	–	54.7 (42.9–65.2)
V10Gy	52.7 (41.3–65.2)	31.2 (19.8–40.3)	42.1 (30.3–51.6)	–	49.0 (38.2–59.2)
V13Gy	48.5 (36.9–60.1)	20.7 (10.1–30.3)	34.2 (25.5–41.2)	–	–
V20Gy	36.7 (27.4–46.7)	7.3 (2.0–14.1)	23.0 (18.3–28.0)	–	43.2 (31.8–54.0)
V30Gy	25.4 (16.7–33.9)	1.4 (0.1–5.4)	14.4 (9.7–18.3)	7.4 (1.2–15.9)	37.2 (24.7–47.7)
V40Gy	–	–	–	4.65 (0.6–9.4)	30.9 (18.1–40.9)
V50Gy	–	–	–	–	28.4 (10.4–32.6)
V60Gy	–	–	–	–	8.6 (1.3–20.7)
Mean dose (Gy)	18.6 (11.7–25.5)	8.1 (4.8–11.4)	13.5 (9.2–17.8)	8.5 [1–16]	23.0 (13.6–32.4)
Max dose (Gy)	67.8 (62.9–69.4)	52.0 (34.7–64.0)	–	–	64.4 (61.0–67.6)
L40Gy (cm)	–	–	–	–	9.70 (4.5–19.3)

Data are shown as median (IQR). VxGy, volume of the organ receiving xGy; IQR, inter quartile range; L40Gy, length of oesophagus receiving 40 Gy.

Table S2 Radiologic toxicity occurring after radiotherapy

Variables	3 months		12 months	
	n=167	%	n=95	%
Alveolar opacities				
Around the tumor	65	38.9	9	9.5
Same lobe	20	12.2	1	1.0
Homolateral lung	11	6.7	1	1.0
Contralateral lung	6	3.3	0	0
Bilateral lungs	4	2.2	0	0
Not reported	61	36.7	84	88.5
Ground glass				
Around the tumor	57	34.4	5	5.3
Same lobe	19	11.1	2	2.1
Homolateral lung	17	10	0	0
Contralateral lung	7	4.4	1	1.0
Bilateral lungs	6	3.3	2	2.1
Not reported	61	36.7	85	89.5
Fibrosis				
Around the tumor	74	44.3	5	5.3
Same lobe	17	10	2	2.#
Homolateral lung	7	4.2	2	2.#
Contralateral lung	0	0	0	0
Bilateral lungs	7	4.2	1	1.0
Not reported	62	37.1	85	89.5
All RILD				
Around the tumor	24	14.4	2	2.1
Same lobe	37	22.2	1	1.0
Homolateral lung	20	12.0	3	3.2
Contralateral lung	9	5.4	1	1.0
Bilateral lungs	15	9.0	3	3.2
Not reported	62	37.1	85	89.5

RILD, radiation induced lung disease.

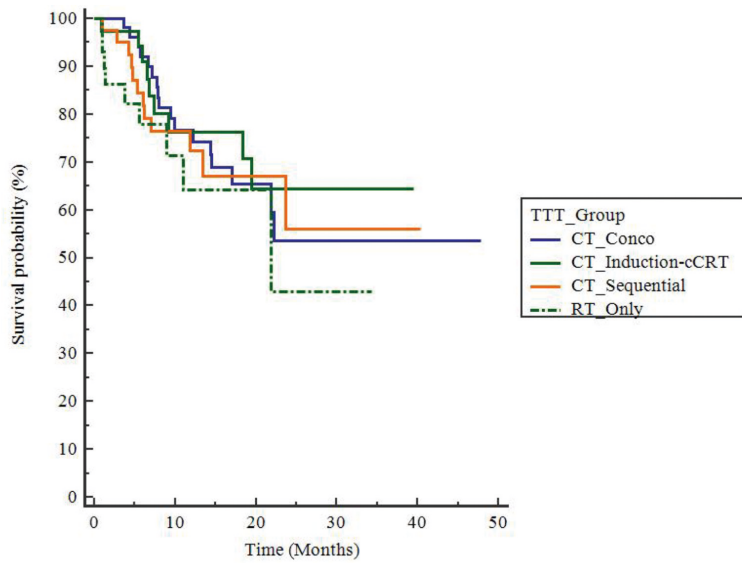


Figure S1 Kaplan-Meier estimate of in field local control in patient receiving radiotherapy only or combined with chemotherapy.

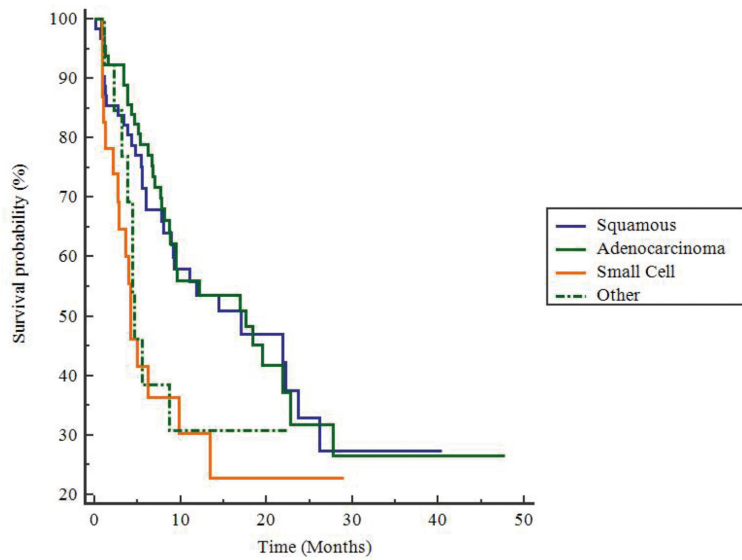


Figure S2 Kaplan-Meier estimate of progression-free survival in patient depending on the histology. Other, large cell undifferentiated carcinoma and giant-cell carcinoma.

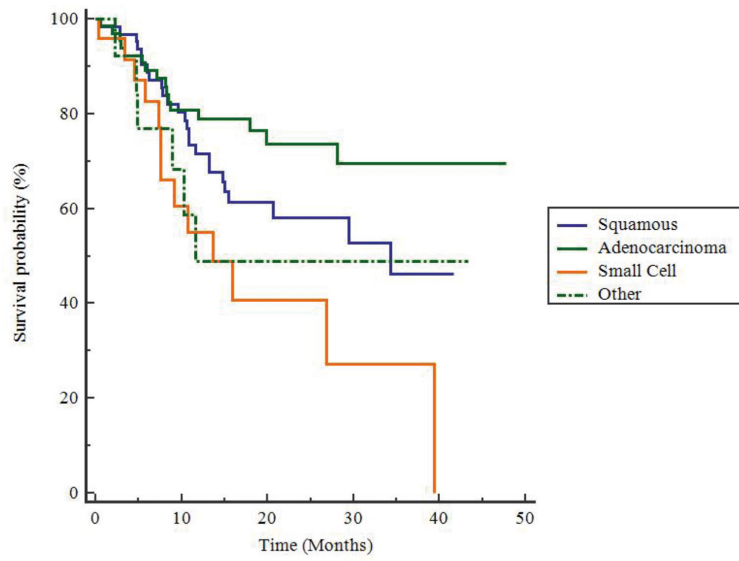


Figure S3 Kaplan-Meier estimate of overall survival in patient depending on the histology. Other, large cell undifferentiated carcinoma and giant-cell carcinoma.

Table S3 Literature data reporting on VMAT and IMRT in lung cancer

Author	n	RT technique	Pulmonary toxicity	Esophageal toxicity	Median FU	Local control
Yom (40), 2007	151	IMRT: n=151	APT: G \geq 3: 8%	N/A	8.5 mo	NR
Sura (41), 2008	55	IMRT	APT: G2: 18%, G \geq 3: 11%; LPT: G2:16%, G 3-4: 2%, G5:2%	AET: G2: 22%, G \geq 3: 4%; LET: G2: 6%, G \geq 3: 0%	26 mo	2 y: 50%
Govaert (42), 2012	86	IMRT: n=86	APT: G 1: 59%, G 2: 23%	APT: G 1: 50%, G2: 35%	N/A	N/A
Jiang (17), 2011	165	IMRT: n=165	APT: G \geq 3: 11%; LPT: G \geq 3: 1%	AET: G2: 70%; LET: G3: 17.6%	16.5 mo	2 y: 57%
Palma (43), 2013	836	IMRT or 3D-CRT	APT: G \geq 2: 29.8%, G5: 1.9%	N/A	2.3 y	N/A
Khalil (9), 2015	87	IMRT: A: 12:V20 <40%; B: 25:V20 <40% + MLD <20 Gy; C: 50: V5 <60%	APT: A: G \geq 3: 42%, G5: 17%; B: G \geq 3: 24%, G5: 16%; C: G \geq 3: 30%, G5: 4%	N/A	18.1 mo	
Wang (32), 2016	327	IMRT: n=152	APT: G \geq 2: 11%, G \geq 3: 3%	AET: G \geq 2:37%, G \geq 3:8%	72.1 mo	5 y: 43%
Wijsman (18), 2017	188	IMRT: n=92; VMAT: n=96	APT: G2: 23.9% vs. 18.8%, G3: 1.1% vs. 0%; LPT: G \geq 3: 9.8% vs. 17.7%	AET: G2: 23.9% vs. 41.7%*, G3:6.5% vs. 17.7%*; LET: G \geq 3: 1.1 vs. 3.1	18.4 mo	
Ling (28), 2016	145	IMRT+IFRT: n=37	APT G \geq 2: 5.4%	AET G \geq 2: 21.6%	13.1 mo	6 mo:76.5%; 1 y:65.8%; 2 y:57.1%
Chun (29), 2017	482	IMRT: n=228	APT G \geq 3: 3.5%	AET: G \geq 3: 13.2 %	21.3 mo	2 y: 30.8%
Ma (44), 2018	150	IMRT n=150	APT: G2: 16%, G \geq 3: 8%	AET: G2: 47.3%, G \geq 3: 24.6%	N/A	N/A
Jaksic (12), 2018	73	IMRT: n=73	APT: G2: 7%, G \geq 3: 6%	AET: G2: 34%, G \geq 3: 1%	44 mo	2 y: 62%
Huang (45), 2018	193	IMRT: n=152; VMAT: n=41		AET: G2: 22.8%, G \geq 3: 4.7%		
Wu (30), 2018	77	VMAT	APT: G2: 16.9%, G \geq 3: 9.1%, G5: 2.6%	AET: G2: 13.0%, G \geq 3: 5.2%	14.8 mo	N/A
Appel (46), 2019	73	IMRT/VMAT (n=22)	APT: \geq G3: 5%	AET: G2-3: 32%, G4: 0%	3.6y	N/A
Rades (31), 2019	278	VMAT	APT: G3: 7.6%			
Zhou (47), 2020	122	IMRT	APT: G3: 20.5%, G4: 3.3%, G5: 1.6%			
Grambozov (48), 2020	72	IMRT	APT: G2: 4.2%, G3-4: 4.2%, G5: 2.8%	AET: G2: 27.8%, G3-4: 11.1%	15.8 mo (0.3–50.5 mo)	1 y: 70%

*, P<0.05. 3D-CRT, 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy; G, Grade; ENI, elective nodal irradiation; IFRT, involved-field radiotherapy; mo, months; y, years; FU, follow-up; AET, acute esophageal toxicity; APT, acute pulmonary toxicity; MLD, mean lung dose; N/A, not available; RP, radiation pneumonitis.