Physics and Imaging in Radiation Oncology 13 (2020) 50–54

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.elsevier.com/locate/phro

Challenges of radical chemoradiation planning in Stage III non-small-cell lung cancer: Can volumetric modulated arc radiotherapy overcome an unfavourable location?

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ARTICLE INFO

Keywords:
Chemoradiotherapy
Locally advanced lung cancer
Radiotherapy technique
Dosimetry

ABSTRACT

Background and purpose: Radiotherapy treatment planning of radical doses for concurrent chemoradiation in Stage III non-small-cell lung cancer (NSCLC) presents many challenges. This dosimetric study aimed to analyse the impact of spatial location of tumour and nodal burden in limiting the achievement of normal organ constraints and the use of appropriate radiotherapy technique to address it.

Materials and methods: Fifteen Stage III NSCLC patients underwent ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) based treatment planning. VMAT (Volumetric Modulated Arc Radiotherapy) plans were made for all patients treated by 3D-CRT (3-Dimensional Conformal Radiotherapy). A binomial logistic regression was performed to ascertain the tumour and nodal characteristics that decreased the likelihood of being planned to 60 Gy.

Results: Inability to achieve normal tissue constraints, particularly spinal cord dose to less than 50 Gy, during initial planning by the assigned treatment technique was the primary dose limiting factor in four patients ($p = 0.02$). Alternate VMAT plans could achieve the dose constraints where 3D-CRT was unsuccessful in patients with bulky central disease in two patients. This technique fell short when there was gross vertebral body erosion.

Conclusions: For tumours with bulky central disease, VMAT should be preferred. With gross vertebral body erosion, even VMAT falls short if the planning target volume includes the spinal cord. In a subset of Stage III NSCLC upfront chemoradiation to radical doses may not be feasible.

1. Introduction

Lung cancer is an aggressive disease with the highest incidence to mortality ratio in 2018 [1]. Non-small-cell lung cancer (NSCLC) comprises of nearly 85% of all cases but irrespective of histology, nearly 35% of all patients are diagnosed in a locally advanced non-metastatic stage. Concomitant chemoradiotherapy has shown to provide better overall survival over induction or consolidative chemotherapy in these patients. The two and five-year survival figures of clinical stage III disease however remain dismal ranging from 55% and 36% (IIIA) to 24% and 13% (IIIC) respectively [2–4].

The limiting factor in delivering radical doses is the close proximity of organs at risk leading to unacceptable toxicities like radiation pneumonitis, esophagitis, cardiac injury and neuropathy. Solutions to improve the therapeutic ratio include advanced radiotherapy techniques and altered fractionation. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) based treatment planning helps in this regard by both better tumour and nodal delineation, thus potentially sparing normal tissue. Multiple studies have shown dosimetric benefits of intensity modulated radiation therapy (IMRT) over 3-dimensional conformal radiotherapy (3D-CRT) but no overall survival benefit has been demonstrated [5–9].

As part of the international collaborative PERTAIN (PET RadioTherApy International, NCT02247713) study, Stage III NSCLC patients were treated with concurrent chemoradiotherapy (CRT) based on PET-CT based imaging in the treatment position. This dosimetric analysis was done on the side-lines of PERTAIN to analyse tumour and nodal characteristics in the subset of patients excluded from the study

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https://doi.org/10.1016/j.phro.2020.03.005
Received 8 January 2020; Received in revised form 16 March 2020; Accepted 17 March 2020

due to inability to plan and deliver doses till 60 Gy in view of critical organ constraints [10]. Alternate Volumetric Modulated Arc Radiotherapy (VMAT) plans were made for patients treated by 3D-CRT to identify the subset of patients where using a different radiotherapy technique might address this shortcoming.

2. Materials and methods

2.1. Patient selection

The 15 included patients were pathologically confirmed, inoperable, Stage III NSCLC patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Informed consent was obtained for all participants. Patients were recruited in the trial after approval from the institutional ethics committee.

2.2. Simulation

A PET-CT was taken in the treatment position under the supervision of a radiation oncologist. Patients with distant metastasis on PET-CT, previous history of thoracic radiotherapy and any uncontrolled comorbidity that could compromise treatment completion were excluded. Patients underwent CT simulation by contrast enhanced 4 Dimensional-Computed Tomography (4D-CT) scans in the same position as the PET-CT within one week.

2.3. Target delineation and treatment planning

Target delineation was done using standard guidelines for PET-CT based target volume delineation [11]. A margin of 6 or 8 mm was given to obtain the clinical target volume (CTV) from the gross tumour volume (GTV) [12]. The 4D-CT took into account the internal target volume (ITV). Hence, a margin of 5 mm was added to obtain the planning target volume (PTV). Both 3D-CRT and VMAT radiotherapy techniques were used based on clinical judgement and resource constraints. Concurrent chemoradiotherapy (CCRT) was delivered for a total dose of 60 Gy using conventional fractionation of 2 Gy per fraction over 30 fractions (6 weeks) with concurrent cisplatin-based chemotherapy. Weekly monitoring of toxicities was done. The cancer stage was restaged as per the 8th edition of the American Joint Committee on Cancer staging [13].

Out of fifteen patients, four could not be planned to 60 Gy due to unacceptable critical organ doses. These included two patients planned by VMAT and another two by 3D-CRT. New VMAT plans of all the patients treated by 3D-CRT (n = 9), both included and excluded patients, were generated for this study. As per the International Commission on Radiation Units and Measurements (ICRU) 50 and 62, the planned treatment delivered at least 95% of the prescribed dose to the PTV [14]. The spinal cord maximum dose was limited to 50 Gy. The lung volume constraints (bilateral lungs minus PTV) were restricted for V5, V20 and Mean Lung Dose (MLD) below 60%, 30% and 20 Gy respectively. The esophagus mean dose was kept < 34 Gy, V35 < 50%, V50 < 40%. For the heart, the mean dose was set at < 26 Gy.

2.4. Evaluation of tumour and nodal characteristics

Descriptive statistics of the tumour and nodal characteristics – volume, spatial anatomical location, invasion of mediastinal structures etc. were generated. The angle of contact of contact of the PTV with the circumference of the vertebral body was calculated for patients where the tumour or nodal mass was in contact with the vertebral body. This angle was defined as the angle subtended by the lines joining the extreme extents of the PTV in the mid-point of the spinal cord.

2.5. Statistical methods

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) v22. Data were expressed as median and interquartile range. Mann Whitney U Test was used to find the difference between groups. To ascertain the effects of spatial location of tumour and nodal burden, a binomial logistic regression was performed with the following variables: tumour volume, nodal volume, angle of contact and mediastinal nodal stage (N3). Level of statistical significance was set at $p < 0.05$.

3. Results

Out of fifteen Stage III patients, mediastinal involvement in the form of tumour extension or nodes or both was present in the majority (n = 12). Similarly, majority had N3 nodal stage (n = 9) which signified a bulky mediastinal disease burden. This was reflected in the number of patients belonging to each composite stage: Stage IIIA (n = 1), Stage IIIB (n = 7) and Stage IIIC (n = 7). On histology, squamous cell carcinomas (n = 12) predominated over adenocarcinomas (n = 3).

Alternate VMAT plans of the nine patients planned by 3D-CRT were generated. Table 1 shows the dosimetric comparison of the median doses between the two. A statistical significance was seen in the form of higher mean dose to heart by 3D-CRT (p = 0.02) and higher V5 of bilateral lungs by VMAT (p = 0.01).

The median doses of critical organs of the patients receiving 60 Gy (n = 11) and those not receiving 60 Gy (n = 4) were compared (Supplementary material, Table S1). Inability to achieve normal tissue constraints, particularly spinal cord dose to < 50 Gy, during initial treatment planning by the assigned treatment technique was the primary dose limiting factor in four patients (p = 0.02).

Out of the four patients who could not be planned to 60 Gy in view of OAR constraints, two were planned by VMAT (Patient 1, 2) and two by 3D-CRT (Patient 3,4). Alternate VMAT plans were generated for the patients 3 and 4 and the dosimetric parameters are outlined in Table 2.

Vertebral body invasion leading to inclusion of the spinal cord in the PTV volume was the dose limiting factor in the two patients treated by VMAT if adequate PTV margins were applied (Patient 1, 2) as shown in Fig. 1(a). Generation of alternate plans to achieve 60 Gy was not successful in this subgroup of patients.

The two 3D-CRT treated patients (Patient 3,4) had bilateral mediastinal lymph nodes (N3) as shown in Fig. 1(b). They were treated with anteroposterior fields to ensure coverage leading to high spinal cord doses. Alternate VMAT plans were made for these patients by which 60 G y could be achieved (Patient 3, 4). one of the four predictor variables (tumour volume, nodal volume, angle of contact, nodal Stage N3) were statistically significant in the binomial regression (p > 0.05).

Table 1
Dosimetric comparison with alternate VMAT plans of the 9 patients treated by 3D-CRT*

OAR		3D-CRT (Gy)	VMAT (Gy)	p
Spinal cord	Dmax	43.9 (32.0–47.7)	39.9 (30.6–44.9)	0.38
Heart	Dmean	15.2 (4.4–34.2)	9.9 (4.6–25.3)	0.02
	V25	23.8 (4.8–54.8)	9.1 (1.7–46.4)	0.07
	V30	19.6 (4.1–36.6)	5.7 (0.8–35.5)	0.08
Esophagus	Dmean	23.3 (15.4–4)	20.9 (19.9–39.9)	0.57
	V35	32 (28.6–74)	31.4 (20.4–55.6)	0.14
	V50	26 (0.8–31.9)	18.7 (3.6–39.2)	0.39
Lung	Mean Lung Dose	14.9 (11.9–20.2)	15.6 (13–20.1)	0.31
	V20	24.9 (22.4–34.9)	27.8 (21.6–42.6)	0.20
	V5	45 (31.3–66)	75.5 (66.8–83.6)	0.01
Conformity Index	CI	0.9 (0.90–0.9)	0.97 (0.9–0.9)	0.08

*Data expressed as median and interquartile range.

Table 2
Organs at risk (OARs) doses of the four patients who did not receive 60 Gy.

Patient number	Total Dose	Technique	V20 lung	V5 lung	Mean Lung Dose	Mean heart	Max spinal cord	Esophagus Mean	Esophagus Max	GTV Nodal volume (cm^3)	GTV volume (cm^3)	PTV Volume (cm^3)
1	56	VMAT	27.7	83.2	14.7	12.3	51.7	29.0	55.3	31.4	50.6	1241
2	54	VMAT	22.8	74	13.0	25.5	44.3	34.2	55.7	12.4	456.4	465
3	50	3D CRT	27.4	47.2	16.1	35.5	55.3	39.8	54.2	18.4	153.1	835
	60	VMAT	44	78	10.8	30	50.7	29.47	62.6			
4	54	3D CRT	15.1	24.9	8.8	1.1	41.1	21.7	54.23	13.9	7.1	612
	60	VMAT	21.9	45.9	10.8	1.4	36	20.9	61.			

However, a trend towards an increasing odds ratio for increasing angle of contact with the vertebral body and inability to plan doses above 60 Gy was observed (Supplementary material, Table S2). Fig. 2 shows the DVH comparing spinal cord doses of the 3D-CRT and VMAT plans in patient 3 having an angle of contact of more than 90 degrees (could achieve dose constraints only by VMAT). None of the four predictor variables (tumour volume, nodal volume, angle of contact, nodal Stage N3) were statistically significant in binomial logistic regression ($p > 0.05$). However, a trend towards an increasing odds ratio for increasing angle of contact with the vertebral body and inability to plan doses above 60 Gy was observed (Supplementary material, Table S2). Fig. 2 shows the DVH comparing spinal cord doses of the 3D-CRT and VMAT plans in patient 3 having an angle of contact of more than 90 degrees (could achieve dose constraints only by IMRT).

4. Discussion

This study investigated the descriptive tumour and nodal characteristics as well as the dosimetric parameters of patients undergoing chemoradiation under the PERTAIN trial which limited 60 Gy treatment planning when rigid OAR constraints were adhered to. With more PET-CT availability, usage of this modality in both staging and treatment planning is on the rise. Preliminary results show a significant improvement in OS (23 months) when compared to historical data by using strictly regulated PET-CT based planning [10].

Concurrent chemoradiation is the standard of care in locally advanced non-small cell lung cancer patients with a satisfactory performance status. The optimal dose required to achieve local control while accounting for manageable toxicity has been investigated thoroughly. Contrary to expectations, a dose of 60 Gy was found to be superior to 74 Gy in terms of survival in the RTOG 0617 trial albeit with some caveats. The survival benefit is offset by the toxicities of chemoradiation if the patient selection is not prudent. The risk of debilitating esophagitis and pneumonitis should be kept in mind while approving treatment plans. Both the total dose and the decision to start upfront chemoradiation is frequently impacted by the tumour and nodal burden relative to the organs at risk [15–18].

Grade 3 esophagitis, the commonest toxicity leading to treatment breaks during chemoradiotherapy, is estimated to be less than 10% in most studies [3,19–22]. Radiation pneumonitis is a potentially fatal toxicity and can be challenging to manage in a subset of patients. Dose volume constraints aimed at keeping the V20 ≤ 30–37% and/or the MLD ≤ 20 Gy results in an estimated radiation pneumonitis rate of 20% or less [23–25]. Irradiation of centrally located tumours lead to increased doses to the esophagus, heart and spinal cord. Two patients excluded from the trial (Patients 3, 4) had centrally located disease and were treated by 3D-CRT. Alternate VMAT plans generated for this study could be made which spared the OARs thus signalling proper technique selection for this subgroup. However, for patients with gross vertebral body invasion (Patients 1, 2) treated upfront by VMAT, no alternate plan could respect the spinal cord doses. Thus a few cycles of upfront chemotherapy maybe an option in these cases.

Comparison of 3D-CRT versus VMAT plans in the 9 patients treated by 3D-CRT showed a statistically significant difference only in terms of increased mean heart doses by 3D-CRT and increased V5 for bilateral lungs by VMAT. Though rates of radiation pneumonitis and radiation esophagitis have been proven to be lower in multiple studies with VMAT, 3D-CRT is the best available option in most LMIC (Low and Middle Income Countries) [7,8,26–28].

Tumour location rather than the volume was associated with a higher likelihood of being a dose limiting factor. Logistic regression did not show a statistical significance which can be explained by the 15 patients though an increasing odds of not achieving 60 Gy was observed with an increasing angle of contact of the PTV with the vertebral body. This problem could be addressed successfully by VMAT plans as evidenced in Patient 3 and 4. Further studies on a larger sample size might help elucidate a threshold angle which will help us choose patients for VMAT over 3D-CRT. Since resource constraints are a major detriment in LMIC, prediction of tumour and nodal parameters that enable a Stage III NSCLC patient to be selected for such an approach and deciding which radiotherapy technique will suffice is necessary.

In conclusion, 3D-CRT is a good option for most patients setting aside the group with a bulky central burden and gross vertebral body contact/invasion. In patients with bulky central disease, VMAT should

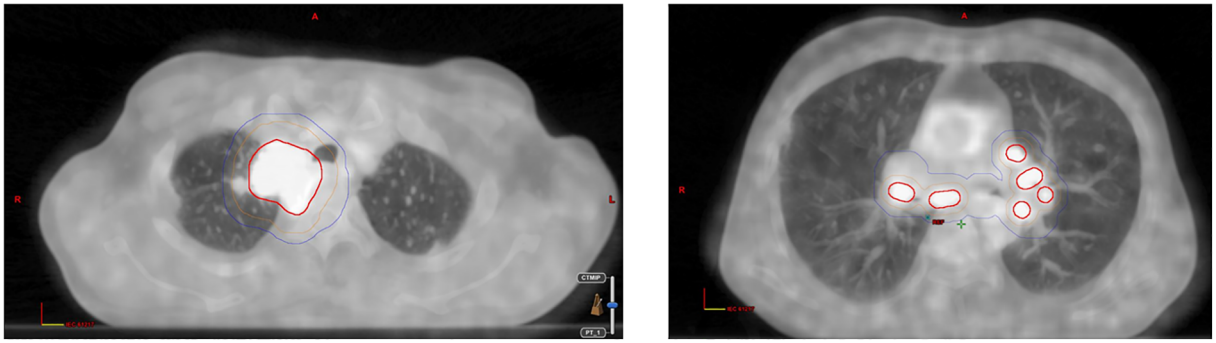

Fig. 1. Spatial location of tumour burden in patients receiving < 60 Gy. (a) Dose received: 56 Gy; tumour encroaching into vertebral body, spinal canal; (b) Dose received: 54 Gy; bilateral bulky N3 nodal burden.

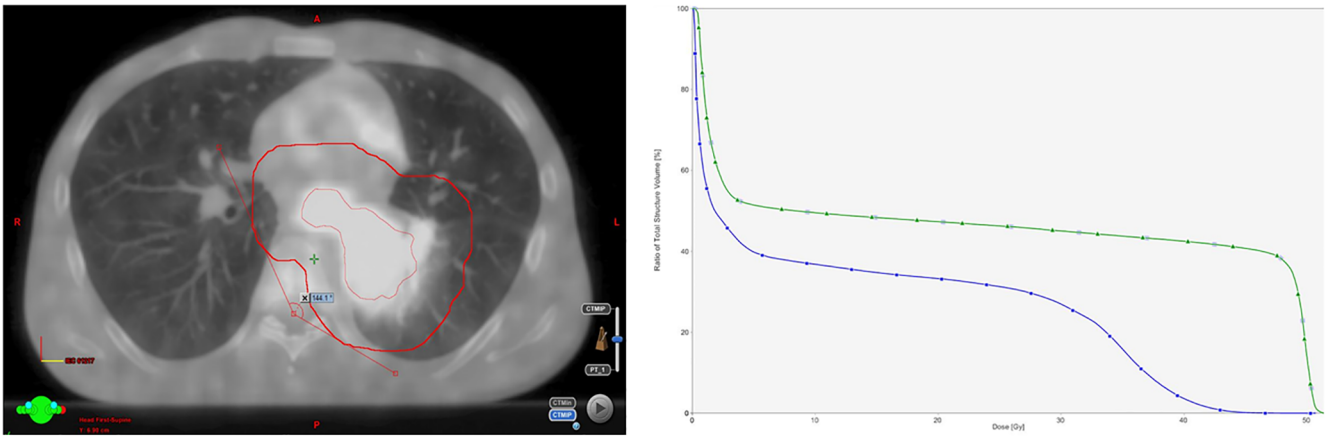

Fig. 2. (a) Tumour with > 90 degrees angle of contact with vertebral body; (b) Comparison of DVH of spinal cord doses between 3D-CRT plans (green) and VMRT (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

be preferred. Identification of the subset of patients not suitable for upfront chemoradiation regardless of technique due to gross vertebral body in the clinics is important.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank Dr. A Polo for giving us permission to publish this article and acknowledge the members of the PERTAIN team: Konert T, Vogel WV, Paez D, Rubio AP, Fidarova E, MacManus MP, Thorwath D, Hanna GG.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2020.03.005.

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