

## Literature Review

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# Is IMRT or VMAT superior or inferior to 3D conformal therapy in the treatment of lung cancer? A brief literature review

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## Abstract

**Aim:** To identify treatment outcome, dose uniformity, treatment time, toxicity among 3D conformal therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT) for non-small-cell lung cancer (NSCLC) based on literature review. **Methods:** A literature search was conducted using PubMed/MEDLINE, BMC—part of Springer Nature, Google Scholar and iMEDPub Ltd with the following keywords for filtering: 3D-CRT, IMRT, VMAT, lung cancer, local control and radiobiology. A total of 14 publications were finally selected for the comparison of 3D-CRT, IMRT and VMAT to determine which technique is superior or inferior among these three. **Results:** Compared to 3D-CRT, IMRT delivers more precise treatment, has better conformal dose coverage to planning target volume (PTV) that covers gross tumour with microscopic extension, respiratory tumour motion and setup margin. 3D-CRT has large number of limitations: low overall survival (OS), large toxicity, secondary malignancies. **Conclusions:** It is difficult to choose the best technique for treating NSCLC due to patient conditions and technique availability. A high-precision treatment may improve tumour control probability (TCP) and patient's quality of life. VMAT, whether superior or not, needs more clinical trials to treat NSCLC and requires longer dose optimisation time with the greatest benefit of rapid treatment delivery, improved patient comfort, reduced intrafraction motion and increased patient throughput compared to IMRT and 3D-CRT.

## Introduction

Lung cancer is the leading cause of cancer deaths in the United States and around the world.<sup>1</sup> Lung cancer causes more deaths in the United States almost every year than prostate, breast, colorectal and brain cancers combined.<sup>2</sup> The American Cancer Society's estimates that for lung cancer in the United States for 2020, there were about 228,820 new cases of lung cancer with 135,720 deaths.<sup>2</sup> The rapid increase in the worldwide prevalence of lung cancer is attributed mostly to the increased use of cigarettes following World War I, though increases in environmental air pollution are suspected to have been a contributing factor as well.

About 85–90% of lung cancers are non-small-cell lung cancers (NSCLC) and 10–15% are small-cell lung carcinoma (SCLC). There are three main types of NSCLC: adeno carcinoma (AC), squamous cell carcinoma (SCC) and large-cell carcinoma (LCC). AC is the most common form of lung cancer found in the outer region of the lung. SCC is found centrally in the lung, where the larger bronchi joins the trachea to the lung, or in one of the main airway branches and is generally linked to smoking. LCC grows and spreads quickly and can be found anywhere in the lung.

It was shown that surgically un-resected NSCLC receiving radiotherapy, after induction chemotherapy, provided a statistically significant survival advantage.<sup>3</sup> The role of radiotherapy in combined modality treatment of locally advanced NSCLC was shown to have significant long-term survival advantages.<sup>4</sup> Addition of radiotherapy to chemotherapy produced local control and survival advantage.<sup>5</sup> Better survival was shown using multi-field conformal therapy without increased toxicity.<sup>5</sup> Due to the proximity of lungs to oesophagus, heart and spinal cord, optimal dose delivery to target volume within thorax is challenging.

For radiotherapy treatment, patients need to be immobilised during the simulation as well as treatment delivery. Computed tomography (CT) simulations providing image sets (slice by slice) are usually used as patient data for treatment planning system (TPS) and dose calculations. PET-CT improves the outline of the gross tumour volume (GTV). Once patient data are acquired, the images are imported in DICOM format for the generation of treatment plan. Different anatomical structures or regions of interest (ROIs) are defined and delineated so that different tissue volume can be identified by the TPS and proceed with the appropriate planning

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procedures. Planning target volume (PTV) that covers clinical target volume (CTV) with a margin of about 2–2.5 cm due to respiratory tumour motion and setup is defined and delineated as a target structure of interest. Heart, breast, oesophagus and spinal cord are the main organs at risk (OAR) for NSCLC treatment. For 3D conformal therapy (3D-CRT) planning techniques, parallel-opposed fields, three fields or two-field wedge pairs, as well as multi-fields are used to cover the size of PTV.<sup>6</sup> MV beams are usually used and conformal treatment blocks are created in the beam's eye view around the CTV with 2.5 cm margin.<sup>7</sup>

Intensity-modulated radiation therapy (IMRT) was first implemented in the early 1990s with the introduction of the first commercial IMRT delivery unit NOMOS Peacock system (NOMOS Corporation, Sewickley, Pennsylvania, USA),<sup>8</sup> when computing capability required for complex inverse treatment planning algorithms became available commercially. The unique feature of IMRT is that the leaves are known as multileaf collimators (MLCs) that help create the complex shape of the beam to conform radiation to the shape of the tumour while minimising exposure of surrounding critical structures. IMRT technology has the ability to treat patients with several different modes that include the complex volumetric-modulated arc therapy (VMAT) mode, when the gantry of the linear accelerator rotates at a constant or variable speed around the patient for a partial or full arc, MLCs are in constant motion and dose rate is continuously varied.<sup>9</sup>

IMRT can be an effective treatment modality for managing advanced-stage NSCLC and SCLC. Target delineation and organ motion due to respiration need to be carefully considered during the simulation. Respiratory motion has a significant impact on the accuracy of tumour targeting with radiation and is of particular interest in the treatment of NSCLC and other thoracic malignancies. With the image-guided radiation therapy (IGRT) technology, 4D-CT treatment planning may be used for radiation dose escalation with tighter radiation fields and has the potential for improving outcomes in patients with thoracic malignancies.<sup>10</sup> Irradiation to uninvolved lung and normal tissues need to be minimised by beam angle selections during planning. In addition to ROIs that are needed to 3D-CRT, IMRT needs inverse planning with fluence optimisation, MLC sequences, beam configuration, plan evaluations, etc.<sup>11</sup>

IMRT plans are usually oriented up to nine beam angles and a low dose 'bath' of radiation is created outside the PTV. This effect (not spread out widely) also occurs in 3D-CRT where only two–four beam angles are usually used. Complex shapes of radiation with IMRT sometimes result in unwanted 'hot spots' or 'cold spots'. Hotspots in OAR put patients at higher risk and cold spots within the PTV under-dose the tumour. IMRT is a technique where hundreds of small radiation beams with different intensities are delivered to provide precise tumour dose while minimising adjacent normal tissue doses and generate a conformal dose distribution with steep dose fall off at the boundary between tumour and normal structures. The aim of this brief literature review is to evaluate, which is the superior radiotherapy technique among 3D-CRT, IMRT and VMAT for the treatment of lung cancer.

## Methods

IMRT usually consists of several treatment fields with different directions, hundreds of beamlets with modulated intensity, an advantage over 3D-CRT, whereas VMAT has an advantage over IMRT due to rotating beam utilisation. A literature search was

conducted using PubMed/MEDLINE, BMC—part of Springer Nature, Google Scholar and iMEDPub Ltd with the following keywords for filtering: 3D-CRT, IMRT, VMAT, lung cancer, local control and radiobiology. Fourteen publications were selected for the comparison of 3D-CRT, IMRT and VMAT to determine which technique is superior or inferior among these three.

## Results

After reviewing different journals and publications,<sup>14</sup> papers were found and reviewed, outcomes of those works are shown in Table 1.

## Discussion

For patients with locally advanced NSCLC treated with concurrent chemotherapy, IMRT had lower rates of severe pneumonitis than that with 3D-CRT.<sup>15</sup> This finding supported routine use of IMRT for the treatment of lung cancer. IMRT showed comparable or better OS compared to 3-D CRT in patients with stage III NSCLC.<sup>17</sup> Also, Harris et al. in a population-based comparative effectiveness study showed that IMRT had similar OS, cancer-specific survival and toxicity risks compared to 3D-CRT.<sup>19</sup> No adequate data were available to determine if IMRT was superior to 3D-CRT in the treatment of NSCLC when similar OS was observed.<sup>23</sup> However, it was shown that IMRT reduced the incidence of grade 2 radiation pneumonitis with increased grade 3 oesophagitis.<sup>23</sup> Both IMRT and 3D-CRT produced comparable pathological and clinical outcomes in another study.<sup>25</sup>

IMRT delivered a higher dose to the target and spared more critical organs than 3D-CRT.<sup>16</sup> However, the utilisation of motion management with 4D-CT-based treatment planning system was crucial for superior IMRT performance. Planning process and treatment delivery with IMRT was time-consuming and placed a strain on valuable resources compared to 3D-CRT.<sup>18</sup> IMRT improved conformity and provided a possibility for dose escalation to tumour, minimising dose to OAR compared to 3D-CRT.<sup>22</sup> IMRT had somewhat better outcomes and because of its good toxicity profiles decreased the probability of developing late side effects or secondary malignancies compared to 3D-CRT. In some patient cases, 3D-CRT technique had an acceptable short-term effectiveness with a mild toxic reaction and improvement of clinical symptoms. IMRT, thus, can be an effective treatment modality and perhaps somewhat superior to 3D-CRT for treating advanced-stage NSCLC.

VMAT provides more conformal radiotherapy with dose escalation to high-risk areas of the tumour and spares more critical structures compare to 3D-CRT. The quality of patient life improved for both IMRT and VMAT with the minimisation of treatment-related toxicities such as pneumonitis and oesophagitis compare to 3D-CRT.<sup>16</sup> With appropriate motion management and plan optimisation, IMRT and VMAT can provide more conformal radiotherapy, achieve better target dose conformity, can spare more critical structures and achieve lower treatment toxicity than 3D-CRT. IGRT and adaptive planning can be useful for minimising target miss and the risk of overdosing critical structures. VMAT requires less number of MUs and shorter treatment delivery time when compared to IMRT. VMAT showed high local control rates and low risk of normal tissue complication in a study by Yamashita et al.<sup>20</sup> Heart dose was reduced in VMAT compared to IMRT. VMAT had superior

**Table 1.** Advantages and disadvantages of 3D-CRT, IMRT and VMAT for NSCLC

Study	Year	Techniques, results, etc.	Summary
Choi et al. <sup>12</sup>	1998	In this study, 95 patients with inoperable NSCLC were entered onto 3D-CRT trial where plans were compared against 2D plans to assess the target volume dose delivery adequacy, dose-volume histograms (DVH) for normal tissue and normal tissue complication probabilities (NTCP). Seventy-eight out of the 95 patient plans were composed of non-coplanar 4–8 multiple fields and the remaining 17 were with co-planar segmented conformal beams choosing gantry angles minimising normal lung exposure.	Comparison of the average NTCP for lung showed a significant difference between patients with and without radiation pneumonitis. 3D-CRT provided superior delivery of high-dose radiation with reduced risk to normal tissue and that NTCP be used as a guideline for the dose escalation.
Yuan et al. <sup>13</sup>	2008	The purpose of this study was to investigate the clinical efficacy and toxic effect of the 3D-CRT for NSCLC. Fifty-two patients with stages I and IV were treated with 3D-CRT. Cross-analysis of the clinical data was conducted in the comparison between 52 cases with 3D-CRT and 50 cases with conventional radiation therapy (CRT). The therapeutic effect was 90.4% (3D-CRT) and 72% (CRT).	The 3D-CRT had a satisfactory short-term efficacy and improvement of clinical symptoms, with a mild toxic reaction and good tolerance in patients. Suggestions were made to use 3D-CRT for enhancing the tumour control rate and bettering the quality of life.
Giraud et al. <sup>14</sup>	2000	The purpose of this study was to quantify microscopic extension (ME) in NSCLC. Seventy surgical resection specimens for which the border between tumour and adjacent lung parenchyma were examined. A total of 354 slides were examined: 176 for AC and 178 for SCC. ME was found different in AC and SCC.	The usual CTV margin of 5 mm appeared inadequate to cover the ME and must be increased to 8 and 6 mm for AC and SCC, respectively, to cover 95% of the ME.
Chun et al. <sup>15</sup>	2017	A secondary analysis was performed to compare IMRT with 3D-CRT in National Research Group (NRG) oncology clinical trial Radiation Therapy Oncology Group (RTOG) 0617, in which patients received concurrent chemotherapy of carboplatin and paclitaxel with or without cetuximab, and 60- versus 74 Gy radiation doses. In this study, the median follow-up was 21.3 months. Of 482 patients, 53% were treated with 3D-CRT and 47% with IMRT. The IMRT group had larger planning treatment volumes, a larger planning treatment volume/volume of lung ratio and more stage IIIB disease.	This study compared 3D-CRT and IMRT outcomes for locally advanced NSCLC in a large prospective clinical trial. Two-year OS, progression-free survival, local failure and distant metastasis-free survival was not different between IMRT and 3D-CRT. The patients treated with IMRT had lower rates of severe pneumonitis than those with 3D-CRT supporting routine use of IMRT.
Chang <sup>16</sup>	2015	IMRT delivered a higher dose to the targets and spared more critical organs in lung cancer than can 3D-CRT. However, tumour motion management and optimised radiotherapy planning based on 4D-CT scanning were crucial to maximise the benefit of IMRT. This article summarised these strategies and reviewed published findings supporting the safety and efficacy of IMRT for lung cancer and discussed the advantages of using IMRT over 3D-CRT. IMRT and VMAT provide more conformal radiotherapy and spare more critical structures than 3D-CRT. IMRT or VMAT do not increase low-dose lung exposure relative to 3D-CRT when lung sparing is considered with appropriate motion management and plan optimisation.	IMRT seems to improve quality of life by minimising treatment-related toxicities such as pneumonitis and oesophagitis. IMRT or VMAT allows further dose escalation within the PTV based on anatomic, biologic and molecular information without prolonging treatment time when integrated boost techniques are used.
Kong and Hong <sup>17</sup>	2016	Randomised trials showing a clear survival benefit of IMRT over 3D-CRT in lung cancer treatment were lacking. This study compared survival rates of patients with stage III NSCLC, treated with either 3D-CRT or IMRT and analysed the prognostic factors for survival. Nineteen patients with IMRT and 30 with 3D-CRT were studied. The choice of treatment type was determined by the physician based on tumour extent and general condition of the patients. The primary endpoint was OS and secondary endpoints were loco-regional recurrence-free survival, distant metastasis-free survival and radiation-induced lung and oesophageal toxicity incidence.	The 1- and 2-year OS rates were 94.7% and 77.1% in the IMRT group and 76.7% and 52.5% in the 3D-CRT group, respectively. IMRT showed comparable or better OS compared with 3D-CRT in patients with stage III NSCLC.
Chan et al. <sup>18</sup>	2014	IMRT added fluence modulation to beam shaping improving dose conformity around the tumour, avoided OAR with lower treatment toxicity. This article discussed challenges in the implementation of IMRT for lung cancer with recommendations of a minimum requirement for safe delivery.	Compared to 3D-CRT, the planning process and treatment delivery with IMRT was time-consuming and placed a strain on valuable resources.

(Continued)

**Table 1.** (Continued)

Study	Year	Techniques, results, etc.	Summary
Harris et al. <sup>19</sup>	2014	The Surveillance, Epidemiology, and End Results (SEER)—Medicare database was used to identify a cohort of patients diagnosed with stage III NSCLC from 2002 to 2009 treated with IMRT, 3D-CRT or 2D-RT. Using Cox regression and propensity score matching, survival and toxicities of these treatments were compared.	In this population-based analysis, IMRT had similar OS, cancer-specific survival and toxicity risks compared with 3D-CRT.
Yamashita et al. <sup>20</sup>	2014	The aim of this study was to report the outcome of primary or metastatic lung cancer patients undergoing VMAT for stereotactic body radiation therapy (SBRT). Lung cancer patients received single arc VMAT using an Elekta Synergy system.	Use of VMAT for SBRT in primary metastatic lung tumours demonstrated high local control rates and low risk of normal tissue complications.
Herman et al. <sup>21</sup>	2010	The purpose of this study was to assess the impact of respiratory gating on tumour and normal tissue dosimetry in patients treated with SBRT for stage 1 NSCLC. Treatment planning of 20 patients was performed using 4D-CT with free breathing, near-end inhalation and near-end exhalation with a prescription dose of 60 Gy in three fractions. The average tumour displacement was 7 mm (lower peripheral lesion), 2.4 mm (upper peripheral) and 2.9 mm (central lesion).	These results indicated that the tumour location is the most important determinant of dosimetric optimisation of SBRT plans. There were no significant differences in tumour and normal tissue dosimetry among three gated plans.
Yegya-Raman et al. <sup>22</sup>	2018	3D-CRT with minimum technological standard for treating NSCLC, allowed for more accurate delineation of tumour by using CT-based treatment planning instead of 2D radiographs.	IMRT improved the conformity over 3D-CRT and provided the possibility for dose escalation to the tumour by minimising radiation dose to OAR.
Hu et al. <sup>23</sup>	2016	There are no adequate data to determine if IMRT is superior to 3D-CRT in the treatment of NSCLC. A meta-analysis was conducted to compare the clinical outcomes of IMRT and 3D-CRT in NSCLC. The OS and relative risk of radiation pneumonitis and oesophagitis were evaluated.	Cox multivariate hazards models revealed that 3D-CRT and IMRT had similar OS; but IMRT reduced the incidence of grade 2 radiation pneumonitis and increased the incidence of grade 3 radiation oesophagitis.
Choi. <sup>24</sup>	2018	The aim of this study was to compare IMRT and VMAT in reducing the dose to uninvolved lungs and heart for advanced-stage NSCLC treatment. Ten patients underwent CT. PTV and OARs were outlined. Five-field coplanar IMRT plans and VMAT plans were generated for each patient. The planning objectives were to minimise the lung and heart dose while maintaining the dose to PTV.	Dose to heart was reduced in VMAT compared to IMRT. Superior delivery efficiency of VMAT, optimised plan quality for DVH and conformity exceeded that of clinical IMRT. VMAT was recommended as a preferred modality for treating NSCLC.
Appel et al. <sup>25</sup>	2019	The aim of this study was to compare IMRT against 3D-CRT in locally advanced lung cancer. IMRT had better normal tissue sparing compared with 3D-CRT. The impact of radiation technique on pathological and clinical outcomes in locally advanced NSCLC was assessed. Concomitant chemoradiation to 60 Gy followed by surgery was used. Pathological regression, surgical margin status, local control rates, disease-free survival and OS between 3D-CRT and IMRT were undertaken.	Both IMRT and 3D-CRT produced comparable clinical and pathological outcomes. This study for the first time validated the real-world effectiveness for IMRT compared to 3D-CRT for locally advanced NSCLC according to pathological specimens in the tri-modality treatment strategy.

delivery efficiency, better optimised plan quality for DVH and conformity. VMAT was, thus, recommended as a preferred modality for treating NSCLC compared to IMRT<sup>24</sup> and of course 3D-CRT.

## Conclusions

At present, most of the lung cancer patients are treated with IMRT and some with 3D-CRT. The use of VMAT to treating lung cancer is very promising; however, it is quite apparent that VMAT, whether superior or not, would need to perform a lot of clinical trials for NSCLC cases. It also ensures to provide low doses to the surrounding organs. Irrespective of which technique (3D-CRT, IMRT, VMAT) one uses, a high-precision TPS will improve TCP and also the quality of life of patients undergoing radiotherapy.

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