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Intensity-modulated radiotherapy, not 3D conformal, is the preferred technique for treating locally advanced lung cancer

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Abstract

When used to treat lung cancer, intensity-modulated radiotherapy (IMRT) can deliver higher dose to the targets and spare more critical organs in lung cancer than can 3D conformal radiotherapy (3DCRT). However, tumor-motion management and optimized radiotherapy planning based on four-dimensional computed tomography (4D CT) scanning are crucial to maximize the benefit of IMRT and to eliminate or minimize potential uncertainties. This article summarizes these strategies and reviews published findings supporting the safety and efficacy of IMRT for lung cancer.

Introduction

Both three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) have been used in the treatment of lung cancer.¹ In 3DCRT, several unmodulated fields (typically 3–4) are designed to deliver dose directly to the targets (Fig. 1). With IMRT, optimized modulated fields (typically 6–12) are designed to deliver the dose to the targets (Fig. 1). The shapes and intensities of each field in IMRT are optimized by means of computer algorithms to conform the dose to the targets and spare the nearby critical structures. Therefore, radiation plans generated for IMRT can deliver higher dose to the targets and spare more critical structures than can be achieved with 3DCRT.^{1–3} Volumetric modulated arc therapy (VMAT) delivers radiation by rotating the gantry through one or more arcs while the radiation beam remains on while simultaneously changing rotation speed, shape of the treatment aperture, and delivery dose rate (Fig. 1). VMAT can deliver highly conformal dose distributions and improve treatment efficiency by reducing the delivery time by up to 50%.^{4,5} Intensity-modulated proton therapy (IMPT) can further improve conformality in that it simultaneously optimizes the intensities and the energies of

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all proton pencil scanning beams by using an objective function that accounts for targets as well as constraints on normal tissues.¹

IMRT, VMAT, and IMPT can all improve the physical and biological dose conformity and allow integrated dose escalation and dose “painting” within the planning target volume (PTV) that collectively lead to the delivery of higher radiation doses to high-risk areas of the tumor such as gross tumor, hypoxic areas or areas showing high standardized uptake values (SUV) on positron emission tomography/computed tomography (PET/CT) without increasing the number of treatment fractions and while minimizing dose exposure to normal tissues (Fig. 2).^{1,7-9} However, several concerns have been raised regarding the use of IMRT, VMAT, or IMPT for the treatment of lung tumors. First, IMRT may deliver more low-dose, yet damaging, radiation to larger volumes of normal lung tissue than is delivered by conventional 3DCRT. Second, tumor movement due to respiration introduces another level of complexity to IMRT, VMAT, or IMPT treatment planning and delivery, as each treatment field may only cover a portion of the target volume at any particular time. A great deal of concern has been expressed regarding the potential for interplay between target motion and collimator motion that degrades planned dose distributions during IMRT or VMAT delivery.¹⁰ In IMPT, dynamic pencil beam delivery and target motion can lead to more severe interplay effects.¹¹ Third, the greater conformity of IMRT, VMAT, or IMPT may result in failures outside of the treatment margin owing to differences in the incidental sterilization of non-targeted lymph nodes. Finally, the lower dose rate of IMRT may be less lethal to cancer cells. These issues are addressed in the following sections.

Optimized IMRT or VMAT Improves Radiotherapy Conformality and Sparing More Critical Structures

3DCRT is highly dependent on beam-angle placement and weights to create uniform intensity to the whole target (Fig. 1). IMRT adds more degrees of freedom, e.g., by modulating the beam intensities, to greatly increase the control over dose distributions, which results in the delivery of higher dose to targets while sparing more normal structures than is possible with 3DCRT.¹⁻³ In designing IMRT plans for lung cancer, beam angle optimization is crucial to spare the critical structures, including lung.¹² Beam configurations depend on target orientation, shape, and size and patient anatomy. The orientation of major tumor and patient anatomy should be considered to ensure the appropriate choice of the preferred beam angles, called the “angle of attack,” for the delivery of IMRT. When sparing of normal lung tissue is a priority, use of anterior/posterior beam angles $\pm 45^\circ$ is preferred; if sparing the heart is a priority then use of a more lateral beam arrangement is preferred. When the dose distribution, especially low-dose regions, is manipulated so as to avoid the lung or heart, target conformity may have to be sacrificed to some extent (Fig. 1). Although this approach may result in reduced conformity to the target and some hot spots or streaks, it may be the only solution to achieve target coverage while maintaining sparing of other critical structures.

A common mistake is to adapt IMRT design strategies from prostate cancer or head neck cancers (the earliest and the most common disease sites for which IMRT was used) for use in lung cancer, i.e., by using multiple beams that are almost evenly distributed over 360° . In

lung cancer, this strategy will significantly increase low-dose irradiation of critical structures such as V_5 of the normal lung that could be detrimental. The priority (i.e., covering target vs. sparing specific critical structures) should be chosen before planning begins based on the individual clinical situation. A balance is always needed between covering the target versus sparing normal tissues. With optimized beam angle and segment design, IMRT can be designed to spare more critical structures than can 3DCRT (Fig. 1). Virtual clinical studies have shown that IMRT treatment plans may be more suitable than 3DCRT treatment plans for patients with advanced-stage disease with large gross tumor volumes (GTVs) and complicated positioning of the tumor within the normal tissue anatomy or for whom sparing the surrounding critical structures from toxicity is of particular concern.^{2,3} Those studies showed that using IMRT led to a median absolute reduction in the percentage of lung volume irradiated to >10 Gy of 7%, and the volume irradiated to >20 Gy was 10%. The volumes of the heart and esophagus irradiated to about 50 Gy and the volumes of normal thoracic tissue irradiated to more than 10-40 Gy were also reduced in the IMRT plans compared with the 3DCRT plans.^{2,3} Moreover, lower-dose (<10 Gy) exposure to the lung could be reduced by limiting the beam arrangements and optimizing the IMRT beam angles.^{2,3}

More recently, IMPT has been shown to further reduce the dose to normal tissues compared with photon IMRT or 3D conformal passive scattering proton therapy and allows radical radiotherapy in clinically challenging cases of stage III, or stage I non-small cell lung cancer (NSCLC).^{13,14} Clinical implementation of IMPT with 4D CT-based motion management and quality assurance has been promising, particularly for re-irradiation and for challenging tumors with complicated anatomy.¹⁵

Motion Management and Adaptive Fractionated Radiotherapy to Minimize Motion Uncertainty in IMRT

Images from 4D CT scans have shown that more than 50% of NSCLC tumors move more than 5 mm during treatment and that almost 11% move more than 1 cm (up to 4 cm), particularly lesions that are near the diaphragm.¹⁶ For patients in whom the tumor moves less than 5 mm, simply expanding the margin of the planning target volume (PTV) is adequate. However, for patients with substantial (>1 cm) tumor motion, an individualized tumor-motion margin and motion-reducing approach such as breath hold or respiratory gated therapy should be considered.¹⁷ Use of 4D CT to account for lung tumor motion in treatment simulation is highly recommended for IMRT, particularly for lesions close to diaphragm. Fractionated radiotherapy is recommended to further reduce the interplay effects in IMRT. A study published in 2002 showed that the main effect of organ motion in IMRT is an averaging of the dose distribution over the path of tumor motion during fractionated radiotherapy rather than systematic errors in dose delivery.¹⁸ Therefore, the final dose delivered to the target and normal tissue should be similar to that for conventional radiotherapy delivered without intensity modulation, and the additional effects specific to the IMRT delivery technique seem to be relatively small. A 4D-CT IMRT treatment planning method that includes a dynamic multileaf collimator motion-tracking algorithm was shown to be sufficiently flexible to account for changes in tumor position during treatment delivery, and could be implemented for clinical purposes soon.¹⁹ Even for IMPT,

the use of 4D CT–based robustness planning with repeated scanning and fractionated treatment can effectively reduce the impact of interplay by averaging out motion-caused effects and thus produce acceptable target dosage.^{15,20} Currently, the Advanced Technology Consortium of the U.S. National Institutes of Health recommends that tumor motion be reduced to <1 cm by using compensation techniques such as breath-hold, respiratory gating, or tumor-tracking techniques if IMRT is to be used (<http://www3.cancer.gov/rtp/imrt.doc>).

Interfractional tumor motion and anatomic changes during the course of radiotherapy, with either 3DCRT or IMRT, could be another cause of target miss or overtreatment of normal tissues in lung cancer.²¹ As a result of these issues, an initial simulation-based treatment plan may not match the treatment delivered. In one study, researchers used weekly 4D CT images to investigate the magnitude of the changes in NSCLC tumor volume and mobility during 7 weeks of radiotherapy.²²

Reductions in tumor volume ranged from 20% to 71%, and tumor mobility significantly increased over this period. In such cases, an explicit initial determination of the internal gross tumor volume (iGTV) may not be sufficient to cover the target. Rather, replanning of radiotherapy by using repeated 4D CT imaging may be warranted for some patients with highly mobile tumors, to reduce the potential for missing the target when using either IMRT or 3DCRT.²²

Clinical Data Supporting the Safety and Efficacy of IMRT for Lung Cancer

Currently no prospective, randomized trial results have been published comparing the efficacy and toxicity of 3DCRT versus IMRT for any thoracic malignancy. However, retrospective clinical reviews from MD Anderson indicate that IMRT can reduce the incidence and severity of pneumonitis and esophagitis compared with 3DCRT in patients with stage III NSCLC undergoing concurrent chemoradiotherapy^{23,24} and may improve survival.²⁵ One comparison of outcomes for patients treated before and after the implementation of IMRT showed no differences in out-of-field, elective nodal, or in-field recurrences.²⁴ Indeed, even with propensity score–matched analyses, no significant differences were found in local-regional relapse, distant metastasis, disease-free survival, or overall survival between treatment groups. Patients who underwent IMRT tend to have fewer episodes of severe acute esophagitis that require the placement of a feeding tube, probably because IMRT allowed the radiation dose to be distributed in a way that reduced esophageal exposure. The benefits of heart sparing could not be accurately analyzed in all the studies noted above owing to the complexity of comorbid conditions and the much longer intervals needed to reveal cardiovascular effects. Another group, at Memorial Sloan Kettering, retrospectively analyzed clinical outcomes after IMRT for lung cancer that involved dose escalation from 60 Gy to 90 Gy. Even though IMRT tended to be used for larger tumors and tumors close to critical organs, IMRT produced favorable local control and survival rates without increasing toxicity.²⁶ Together, these findings suggest that the theoretical concerns regarding the use of IMRT for lung cancer do not affect clinical outcomes, provided that strict quality assurance and compensation for respiratory motion are rigorously applied.

Also of note, oft-cited concerns that IMRT may result in increased pulmonary toxicity by exposing large amounts of lung to “low-dose baths,” increased regional lymph node recurrences because of reduced incidental doses, or reduced overall local control because of lower dose rates have not been validated in any of the clinical studies done to date.

Another approach to comparing treatment toxicity from IMRT and from 3DCRT is population-based analysis of large databases. In two such analyses of the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, rates of esophageal and lung toxicity were similar after IMRT or 3DCRT.^{27,28} However, these results must be interpreted cautiously because toxicities are not always recorded accurately or consistently in national databases.

Another form of comparison comes from a recently closed phase III multi-institutional randomized study comparing two doses of radiotherapy (74 Gy vs. standard 60 Gy) with concurrent chemotherapy with or without cetuximab for stage III NSCLC (RTOG 0617), in which about half of all patients received IMRT and the other half received 3DCRT, at the discretion of the treating physician. The two groups were well balanced in terms of patient characteristics except that the IMRT group tended to have larger tumors.²⁹ A preliminary report of patient-reported quality of life from that trial suggested that patients (although not care providers) found that quality of life was better after IMRT than after 3DCRT. These are the first prospective findings to support the idea that IMRT can reduce treatment toxicity and improve quality of life.

Work Flow and Delivery of IMRT, VMAT, and IMPT

The greater complexity and sophistication of IMRT or VMAT treatment planning compared with that of 3DCRT planning may lead some to assume that implementation of IMRT-based treatment for lung cancer would impede dosimetric workflow. However, knowledge-based IMRT autoplanning systems can be used to automatically set up IMRT beams, set inverse planning initial conditions and initiate the optimization process, automatically adjust inverse planning parameters based on objective cost functions, and finally generate high-quality “auto-IMRT” plans.³⁰ With the continued maturation of optimization algorithms and automated planning software, IMRT planning can actually save time compared with 3DCRT planning, especially for complicated cases.

As alluded to earlier, VMAT can deliver radiation more efficiently than fixed-field IMRT.^{4,5} The shorter treatment time of VMAT can increase patient throughput, reduce the risk of intrafraction motion, and improve patient comfort during treatment. The major challenge with designing VMAT treatment plans in current clinical practice is that VMAT requires more time to optimize than IMRT, which may introduce more variations in plan quality because of limits on planner time and effort. Hence assurance of high-quality treatment plans is more difficult for VMAT than for IMRT. Again, one study showed that optimized VMAT autoplanning systems can improve the efficiency of VMAT treatment planning and can ensure high-quality VMAT plans for patients with stage III lung cancer.⁵ In addition, VMAT plans were comparable to or better than IMRT in terms of maintaining target coverage and sparing critical structures (Fig. 1).

Finally, early development of clinical guidelines for the implementation of IMPT for lung cancer have shown promising early results, particularly for recurrent disease.¹⁵

Conclusions

1. With appropriate motion management and plan optimization, IMRT, VMAT, and IMPT can provide more conformal radiotherapy and can spare more critical structures (e.g., lung, heart, esophagus) than can 3DCRT or passive scattering proton therapy. IMRT or VMAT does not increase lung low-dose exposure of the lung relative to 3DCRT when lung sparing has been taken into consideration.
2. Interplay effects of IMRT, VAMT, and IMPT can be minimized with the use of motion management techniques and fractionated regimens.
3. Image-guided radiotherapy and adaptive replanning can be useful for minimizing target miss and the risk of overdosing critical structures in selected cases in which tumor motion or size or patient anatomy change substantially over the course of radiotherapy.
4. IMRT does not compromise local-regional control when doses similar to those used for 3DCRT are delivered to the PTV.
5. IMRT seems to improve quality of life for patients with NSCLC by minimizing treatment-related toxicities such as pneumonitis and esophagitis.
6. IMRT, VMAT, or IMPT can allow further dose escalation within the PTV based on anatomic, biological, and molecular information without prolonging treatment time when integrated boost techniques are used (Fig. 2).

In summary, these sophisticated radiation techniques (IMRT/VAMT/IMPT) offer unique research opportunities and possibly a means of improving the therapeutic ratio of radiation for lung cancer. These approaches may well translate into improve local control and potentially improved survival without increasing treatment-related toxicity. When this article was written, we have seen what 3DCRT can do, but we have yet to see all of what IMRT, VMAT, and IMPT can do. Now is the time to use and compare the effects of intensity-modulated radiotherapies, including regular photon IMRT, VMAT, and IMPT, for the treatment of lung cancers.

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Recommendations for the Clinical Implementation of IMRT and VMAT

1. 4D CT-based motion analysis and management is highly recommended to account for tumor motion, particularly for tumors that move by 1 cm or more.
2. Optimized IMRT or VMAT planning that uses “angle of attack” beams is recommended to prioritize the sparing of specific normal tissues while maintaining appropriate target coverage.
3. Quality assurance and delivery verification are absolute requirements for all IMRT cases.
4. Adaptive replanning may be indicated for selected cases if tumor motion or anatomy has been significantly affected during radiotherapy, so that sparing of normal critical structures and adequate target coverage can be maintained.

Figure 1.

Intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) can spare more critical structures than can three-dimensional conformal radiotherapy (3DCRT) in the treatment of a bulky stage III non-small cell lung cancer (NSCLC) tumor located near the esophagus and heart. *Top row*, 3DCRT cannot safely be used to deliver a definitive dose (60 Gy) because it results in an unacceptably high total mean lung dose (21 Gy), heart dose ($V_{40}=43\%$). *Second row*, Limited intensity modulation using the same four beam angles as are used in 3DCRT (IMRT-3D; dashed lines) resulted in improved sparing of lung, heart,

and esophagus, particularly in the low-dose region. Although IMRT-3D is not an ideal solution in this case, IMRT-3D could be similar to or better than 3DCRT in terms of sparing critical structures if the same beam angles are used. (Even in the worst case, one can always choose to not modulate intensity if that would increase the dose to critical structures of interest.) *Third row*, Optimized IMRT using 9 beam angles (IMRT-Op) further improves sparing of critical structures, particularly the heart. Note that target conformality is compromised in IMRT-Op in order to spare more heart and contralateral lung. *Bottom row*, Optimized IMRT (9 beam angles) and VMAT (2 arcs) produce similar critical normal tissue sparing in this case.

Figure 2.

Intensity-modulated radiotherapy (IMRT) with a simultaneous integrated boost technique was used to deliver 69.6 Gy to the gross tumor volume (GTV) and 60 Gy to the planning target volume (PTV) in 58 fractions, given twice a day over 29 days, with concurrent chemotherapy for a patient with stage IIIB right superior sulcus squamous cell lung cancer that was causing severe pain and paralysis of the right arm. *Panel A*, Axial (*top left*), coronal (*top middle*), and sagittal (*top right*) computed tomography (CT) scans illustrate IMRT treatment plans in which 7 non-coplanar beams are aimed at the target. *Panel B*, Positron emission tomography (PET)/CT scans before treatment (*left*) and at 1.5 years after treatment (*right*) illustrate complete response, with resolution of symptoms.