Review Article

The radiation techniques of tomotherapy & intensity-modulated radiation therapy applied to lung cancer

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Abstract: Radiotherapy (RT) plays an important role in the management of lung cancer. Development of radiation techniques is a possible way to improve the effect of RT by reducing toxicities through better sparing the surrounding normal tissues. This article will review the application of two forms of intensity-modulated radiation therapy (IMRT), fixed-field IMRT and helical tomotherapy (HT) in lung cancer, including dosimetric and clinical studies. The advantages and potential disadvantages of these two techniques are also discussed.

Keywords: Lung cancer; radiotherapy (RT); intensity-modulated radiation therapy (IMRT); helical tomotherapy (HT)

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Introduction

Radiotherapy (RT) plays an important role in the management of lung cancer. The dose-response effect for local control in non-small cell lung cancer (NSCLC) has been early demonstrated (1-4), which was also reflected in the treatment of early stage NSCLC with stereotactic body radiotherapy (SBRT) based on a regression analysis of clinical reports from several institutions on the treatment of 92 lesions (5), and the fact that a biologically effective dose (BED) of above 100 Gy was required for optimal local control (6). However, in the recent trial of the Radiation Therapy Oncology Group (RTOG) 06-17 (7), when applied concurrent chemoradiotherapy with a higher radiation dose of 74 Gy did not benefit overall survival (OS) as compared to the lower dose of 60 Gy. Although the results from RTOG 06-17 are inconclusive due to the short follow-up time, higher toxicities by the higher dose has been assumed to possibly produce such a consequence (8). Lung tumors are surrounded by highly radiosensitive tissues, so the normal tissue toxicities associated with RT could inevitably influence the overall treatment outcomes. Development of radiation techniques is a possible way to improve the effect of RT by reducing toxicities through better sparing the surrounding normal tissues. In general, RT has moved from simple two-dimensional to three-dimensional delivering techniques during the past several decades, with the first introduction of three-dimensional conformal radiation therapy (3D-CRT), and then intensity-modulated radiation therapy (IMRT).

IMRT, representing the most advanced radiation technique, has been shown to produce more conformal dose distribution, and better normal tissues sparing when compared to 3D-CRT. There are several approaches can be used to deliver IMRT (9). Fixed-field IMRT, delivered using conventional clinical linear accelerators fitted with multileaf collimator (MLC), has become the most common form of IMRT, which is also considered as the standard form of IMRT and always referred to as IMRT routinely. Helical tomotherapy (HT), another mode of IMRT, which can deliver RT with rotational fields, has been more and more popular recently. The main focus of this article is

the application and comparison of these two approaches, fixed-field IMRT and HT, in lung cancer. For brevity, we will use the term IMRT to refer to fixed-field IMRT in the remainder of the document unless otherwise necessary for clarity.

Brief introduction of IMRT and HT techniques

Intensity-modulated radiation therapy (IMRT)

IMRT, delivered by standard clinical linear accelerators, was developed based on 3D-CRT, in which a finite set of fixed angle/direction beams (fields) are utilized, and the beam-eye-view (BEV) projection of each beam should cover the planning target volume (PTV). However, differing from 3D-CRT, each beam are subdivided into a regular set of beamlets in IMRT and the radiation intensity of each beamlet is controlled by MLC, thus the dose profiles delivered by each of these beams are modulated by essentially superposing many sub-beams or segments (10,11). Because the volume to be irradiated may, of course, include critical organs and we wish to minimize the doses delivered to these structures, IMRT can offer more degrees of freedom to reach the ideal dose distribution wanted.

Helical tomotherapy (HT)

HT shares similar technology with spiral computed tomography (CT) scan (12,13). A small radiation source, which is a 6 MV linear accelerator, was mounted on a CT ring gantry. The geometry provided the opportunity to provide treatment utilizing the continuous spiral 360 degree rotation of the CT gantry, where radiation is delivered helically through 51 projections per rotation. The MLC has two sets of interlaced leaves that move in and out very quickly to constantly modulate the radiation beam as it leaves the accelerator. Meanwhile, the patient is slowly and continuously translated through the bore as the gantry rotates. So each time the linear accelerator comes around, the beam is directed at a slightly different plane, radiation dose is modulated at every angle to conform to the target. Typically, tens of thousands of beamlets are included in one treatment session. A single beamlet corresponds to the radiation emitted through an open leaf of the MLC with the gantry at any given angle, during any given rotation.

The expectation of HT lies in the intuitive argument that the patients treated with 51 equally spaced beam directions per gantry rotation instead of choosing a fixed-beam setup will produce 51 individual intensity modulation patterns over a single gantry rotation, which may allow a much greater degree of freedom in the modulation because of the significant increase in the number of beamlets. Over the last decade, many studies (14-18) have been conducted to explore the effects of varying the numbers of beams used in fixed-field IMRT plans and the angles from which those beams are directed. Their main findings are that the dose distributions can be improved by appropriately increasing beams in combined with optimizing beam angles. HT planning can be viewed as a process that optimizes the influence of a large number of equispaced coplanar fixed fields and thus essentially intrinsically optimizes coplanar beam angles.

The same linear accelerator of HT can also be used for obtaining MVCT images prior to actual daily fractionated treatment. The availability of daily MVCT guarantees an accurate repositioning of the patient before irradiation: after the matching between the simulation CT and the daily MVCT, patient position can be corrected considering bony anatomy and/or tumor position (19-21). In addition, the image-guided adaptive RT based on information obtained from MVCT images will become more practically (22,23).

Data from dosimetric studies

IMRT versus 3D-CRT

Grills *et al*. (24) analyzed the potential for reduced toxicity and increased prescribed dose in 18 inoperable stage I-IIIB NSCLC patients with a prescribed dose equal to 70 Gy. In node-negative patients, IMRT and 3D-CRT offered similar results in terms of mean lung and esophageal normal-tissue complication probability (NTCP); in node-positive (stage IIIA/B) patients, IMRT was beneficial when compared with 3D-CRT, with the advantages that IMRT reduced the lung V20 and mean dose by approximately 15% and lung NTCP by 30%; while meeting all the normal tissue dose constraints, IMRT increased the deliverable dose 25-30% over 3D-CRT in node-positive patients; in the special cases where the gross tumor volume was close to the esophagus, IMRT reduced the mean esophagus V50 by 40% (*vs*. 3D-CRT) and the esophageal NTCP was at least doubled converting from IMRT to 3D-CRT. In a planning study (25) from MD Anderson Cancer Center (MDACC) in comparing 3D-CRT and IMRT for 10 stage I-IIIB NSCLC patients, the V10 and higher dose volumes were reduced in most of the cases using IMRT but not V5;

V20 had a median reduction of 8% and the amount of lung V5 in IMRT increases with the number of fields; similar to the study by Grills *et al*. (24), when the complexity of target volumes increases, the difference between IMRT and 3D-CRT becomes even more significant in favor of IMRT. So a subsequent dosimetric study with larger patient number was performed in MDACC, IMRT plans were generated for 41 patients with recurrent or Stage III-IV NSCLC who had undergone 3D-CRT. IMRT planning produced median absolute reductions in the relative percentages of normal lung volume irradiated to >10 and >20 Gy of 7% and 10%, respectively, corresponding to a decrease of >2 Gy in the total lung mean dose and a significant decrease in the model-based risk of treatment-related pneumonitis, however, a marginal increase occurred in the spinal cord maximal dose and lung volume >5 Gy in the IMRT plans, which could be have resulted from the significant increase in monitor units and thus leakage dose in IMRT (26).

HT versus 3D-CRT

A virtual study by Scrimger *et al*. (27) was performed to compare 60 Gy HT and 3D-CRT plans calculated for five patients with stage III inoperable NSCLC, using dose-volume histogram (DVH) reduction techniques, including mean normalized dose (NTD_{mean}), V20, and effective uniform dose (EUD). The results showed that the NTD_{mean} of both lungs was significantly reduced in all cases when using HT planning (range, 10-53% reduction; mean, 31%); the V20 was also reduced in all cases using tomotherapy (range, 17-37% reduction; mean, 22%); for a constant lung NTD_{mean}, it should be possible to increase tumor dose to up to 160 Gy in certain patients with HT. Another comparison between HT and 3D-CRT was made by Cattaneo *et al*. (28) in thirteen locally-advanced NSCLC in terms of DVH and NTCP. They found that HT significantly improved dose homogeneity within PTV compared with 3D-CRT. For lung parenchyma V20-V40 were lower with HT, corresponding to a decrease of 7% in the risk of radiation pneumonitis, but in the low dose region (<15 Gy) of lung DVH, the difference between HT and 3D-CRT decreased; the mean V5 with HT was higher than with 3D-CRT (70.4% *vs*. 67.4%) but the difference was not statistically significant. The volume of the heart and esophagus irradiated to >45-60 Gy were reduced using HT plans; for eight patients with an esophagus-PTV overlap >5%, HT significantly reduced both late and acute esophageal complication probability.

HT versus IMRT

As many planning studies have demonstrated the theoretical dosimetric advantages of IMRT over 3D-CRT, especially in the complex lung cases, the dosimetric comparison between HT and IMRT mainly focused on the more complex lung cancer patients such as the ones with large and/or centrally located lesions or for patients who have widespread lymph node involvement. HT plans have been created by Kron and colleagues (29) for 15 patients with stage III inoperable NSCLC, and compared with IMRT plans generated using 6 to 10 coplanar beams sometimes equally spaced and sometimes adjusted to reflect the topology of the target and critical structures. In order to provide the most challenging scenario, all patients were planned to receive 60 Gy at the primary target and 46 Gy at the regional lymph nodes, including the mediastinum. A dose quality factor (DQF) which was defined for representing the whole treatment by simultaneously considering both the target and organs at risk was used for characterizing the quality of the treatment plans. A good correlation was found between the quality of the HT plans and the IMRT plans with HT being slight better than those of the IMRT in most cases. The overlap between lung and PTV was found to be a good indicator of plan quality for HT. Another comparative planning study (30) from China comprised 10 NSCLC patients (1/10 staging IIB, 5/10 staging IIIA, 4/10 staging IIIB). They found the dose coverage, conformity, and homogeneity of the targets' volumes were satisfactory in both plans, but the homogeneity of the HT plan was better than that of IMRT; the high-dose radiation volume (V20-V30) to the lung and the mean lung dose (MLD) decreased ($P<0.05$), but the low-dose radiation volume (V5-V10) increased slightly in the HT plan ($P>0.05$); the maximum doses to the spinal cord, heart, esophagus and trachea in the HT plan were lower than those in the IMRT plan, but the differences were not statistically significant. A study performed by Mavroidis *et al*. (31) aimed to compare 3D-CRT, IMRT and HT in lung cancer RT based on radiobiological measures. Only four patients were included and the applied plan evaluation method showed that using both physical and biological criteria, 3D-CRT has a poor expected clinical outcome compared with the HT and IMRT plans; the IMRT plan is more effective than the respective HT over the clinically prescribed dose region; treatment plans delivering low integral doses to the healthy tissues and fairly homogeneous doses to the ITV can be produced either by HT and/or IMRT radiation modalities. However, the results should be interpreted with caution that very few cases

were included and the accuracy of the radiobiological model need to be validated clinically.

Summary of the findings from dosimetric studies

Compared with 3D-CRT, the advantages of IMRT and HT for the treatment of lung cancer are manifested mainly in improving the conformity and uniformity of the target and significantly reducing the radiation doses for the organs at risk, especially the MLD and V20 for the lung, but at the cost that more low dose area spread to the normal lung and more integral doses to the healthy tissues. The advantages of IMRT and HT over 3D-CRT are more pronounced in the complex lung cases. In comparison to IMRT, the HT may slightly improve the planning quality for selected cases, such as the large overlap of PTV and lung, the near distance between target and adjacent critical organs, but the low-dose spread effect will be more notable due to its delivering method.

Potential disadvantages of IMRT and HT

There are some concerns with respect to the use of IMRT, including fixed-field IMRT and HT, in lung cancer.

Low-dose radiation exposure of normal lung and other tissues

Lung is a radiation-sensitive organ, which is supposed to be damaged by the low dose radiation. In rat experiments, it was shown that changes in pulmonary function could be observed in the case of irradiation of large lung volumes to low doses (32). Gopal *et al*. (33) reported losses in the diffusing capacity of carbon monoxide in lung exposed to low-dose radiation. This low-dose radiation effect could be more pronounced when combined modality, such as concurrent chemoradiotherapy would be used (34). The MD Anderson group (35) reported that the absolute volumes of total lung receiving less than 5 Gy is an independent predictor for pulmonary complications in esophageal cancer patients treated with postoperative concurrent chemoradiotherapy with IMRT. Another study (36) also from MD Anderson showed V5 was the only significant factor associated with the treatment-related pneumonitis in NSCLC patients treated with concurrent chemoradiotherapy. Thus a general problem of all IMRT is that target dose distributions are improved and hot spots in normal structures are reduced both at the expense of radiation delivered to larger volumes of normal structures, including lung and other tissues; this "dose dumping" is of concern particularly in HT where radiation is given from 360°, which has been demonstrated in the dosimetric studies. Lung volumes receiving low doses can be reduced by limiting beam numbers with careful selection of beam angles and the use of different dose objectives (25,37) in the case of IMRT, and maybe the use of partial rotation in HT treatment. But more clinical data are needed in order to improve the understanding low-dose irradiation effects and their influence on the optimal choice of dose plan.

Using IMRT or HT, the total absorbed dose to the individual, called the integral dose, will be much higher as compared with conventional radiation treatments, resulting from scattering and leakage radiation. Following exposure to low dose radiation there is a increased risk of radiation-induced second malignancies years or even decades following treatment (38). Hall and Wuu reported that IMRT induces almost double the incidence of second malignancies compared with 3D-CRT (39). HT machine has a 22 cm of tungsten shielding in primary jaws, the MLC, and head shielding (40). Because of the maximize beam shielding for radiation leakage in HT comparing to the conventional linear accelerators to give rise to lower scattered dose. Although the detailed information regarding the radiation-induced malignancies by using IMRT and HT is rare, more caution should be given when the patients have long life expectancy and especially the patients are pediatrics or young adults (41,42).

Interplay effects

In 3D-CRT, the whole target is typically covered by the treatment beams from any treatment directions where the uncertainties from target motion may be accounted for by introducing ITV margin. However, the IMRT treat only a part of the target at any specific time using the dynamic delivering modes, thus the so-called interplay effects caused by the interplay between the moving target in the patient and the dynamic dose delivery may result in target under-dosing.

Interplay effects in IMRT

Interplay effects in fixed-beam IMRT was studied theoretically by numerous authors (43). Yu *et al*. (44) simulated the dose delivery by a slit beam moving at a across a 30-cm long target plane that moves sinusoidally, in which the cumulative primary photon fluence delivered to

the plane was calculated and used to evaluate the interplay effect. They found that the interplay effect strongly depends on the speed of the slit beam relative to that of target motion and beam width, the dose deterioration increased with the increase of the relative speed and decrease of the beam width; they also studied the influence of fractionation on the interplay effect and found the delivered dose error was reduced when fractionation was considered. The findings of Yu *et al*. (44) were validated by Bortfeld *et al*. (45) with a mathematical statistically model. Jiang *et al*. (46) performed an experimental study on the magnitude of the interplay effect in lung IMRT treatments, as well as its dependence on the delivery mode, dose rate, collimator angle, and motion starting phase. A solid water phantom with an embedded ion chamber was placed on a motor-driven sinusoidally moving platform which was used to simulate the tumor motion, and the physical parameters from two 5-field IMRT plans for the actually treated lung cancer patients were applied. For each field, the measurement was made for 2 dose rates (300 and 500 MU/min), 3 MLC delivery modes (sliding window, step-and-shoot with 10, and 20 intensity levels), and 8 uniformly spaced initial motion phases. It was found that the dose from one field averaged over various initial phases only differs by a few percent from the corresponding static dose, whereas the maximum dose variation for just one phase can be up to 30% of the static dose. However, the maximum dose variation is reduced from 30% for one field of one fraction to 18% for all 5 fields after one fraction and further reduced to less than 1% to 2% after 30 fractions. They also found the dose variation decreases with decreasing dose rate (increasing delivery time).

Interplay effects in HT

Interplay effects in tomotherapy delivered with HT beam and sequential tomotherapy beam were measured by Yang *et al*. (47), using a computer-controlled dynamic phantom to simulate longitudinal tumor motion. They found that the dose uniformity perturbation was not significant at the typical breathing frequency and amplitude in HT delivery; the heterogeneity caused by respiratory motion is small when beam rotation time is much longer than the 'breathing' period of the phantom, the 'breathing' amplitude is smaller than 1 cm, and the beam modulation caused by nearby critical structures is absent. Kanagaki *et al*. (48) also performed a phantom study to determine the dosimetric effects of motion upon actual HT treatment delivery with the film dosimetry measurements under static and moving conditions using a clinical HT treatment unit. The motion phantom system was constructed using a programmable motor, a base, a moving platform and a life size lung heterogeneity phantom with wood inserts representing lung tissue with a 3.0 cm diameter spherical tumor density equivalent insert; the effects of varying target motion amplitude and periodicity, HT jaw width, couch speed and gantry rotation speed parameters were used to measure CTV dosimetric coverage in the hopes of finding combinations that can cause adverse synchronization and gross CTV under-dosing. It was found, although the phantom motion and HT delivery is mechanically periodic and only one fraction was delivered, no gross dose heterogeneity from interplay of these two moving components was measured; significantly different results by using different jaw sizes in HT delivery with a larger jaw size is less susceptible to the effect of motion, and they concluded that HT is a safe technique for treating moving tumors even with hypofractionation. Kissick *et al*. (49) analyzed the interplay effects by the use of longitudinal simulations of mock and surrogate data and tested with a fully 4D HT delivered plan and found the acceptable influence for typical breathing patterns and magnitudes.

Summary of the interplay effects in IMRT and HT

In IMRT, a gross error can result from interplay effects, but the magnitude of the error tends to diminish with increased fractionation, using multiple fields, and randomness of the synchronization between treatment delivery and breathing phases. In HT, dosimetric impacts of interplay effects are not significant for typical breathing patterns and magnitudes, even when only one fraction was delivered, thus HT could be considered as a safe irradiation technique for treating moving targets. However, it should be noted that those simulations were performed using somewhat simplistic sinusoidal tumor motion models. Real patient breathing cycles sometimes exhibit complicated patterns, with continuously changing amplitude and periodicity (50,51), so the approaches to reduce the respiration-induced motion and real-time image guidance, such as breathing holding , gating or tracking techniques, should be considered to fully use the potential of IMRT in lung patients.

Clinical data

There have no randomized trials comparing the clinical outcomes of 3D-CRT and IMRT in lung cancer till now (52). Two retrospectively comparative studies were

performed in MDACC: Yom *et al*. (53) compared 68 patients treated with IMRT to 222 patients treated with 3D-CRT to median doses of 63 Gy. Despite the IMRT group's larger gross tumor volume (194 *vs*. 142 mL, P=0.002), the rate of grade ≥3 pneumonitis at 12 months was 8% compared with 32% for 3D-conformal (P=0.002); the study by Yom *et al*. (53) was expanded upon by Liao *et al*. (54) who retrospectively analyzed the treatment outcomes of 318 NSCLC patients treated with 3D-CRT and 91 NSCLC patients treated with IMRT. In that study, the median OS times were 1.4 years for IMRT group and 0.85 years for 3D-CRT group, and OS was significantly better in patients treated with IMRT. Recently, two population-based comparative studies (55,56) regarding IMRT in stage III NSCLC based on the Surveillance, Epidemiology, and End Results (SEER) database were published: the study by Shirvani *et al*. (55) mainly focused on the toxicities and found that esophagus and lung toxicity rates were similar between IMRT and 3DCRT; in another study (56), both treatment outcomes and toxicities were analyzed, with the findings that IMRT was associated with improved OS [hazard ratio (HR) 0.90, P=0.02] and cancer-specific survival (CSS) (HR 0.90, P=0.02) in univariate analysis, but was associated with similar OS (HR 0.94, P=0.23) and CSS (HR 0.94, P=0.28) in multivariate analysis compared with 3D-CRT, and the similar toxicity risks occurred in both groups. Because of the non-randomization nature, the two SEER database studies (55,56) should be interpreted with caution: firstly, the patient treated with IMRT tend to have more complex lesions such as large tumor volumes and more extensive lymph nodes (53,54); secondly, the study period captured the earliest use of IMRT in most institutions with rare experience, but the 3D-CRT was the mature standard-of-care for lung cancer at that time; thirdly, the imperfectly records in SEER-Medicare data, especially the toxicities, would confound the analysis. Shirvani *et al*. (57) conducted a retrospective comparison of IMRT and 3D-CRT for stage I-III small cell lung cancer and found decreased use of tube feeds with IMRT but similar rates of intravenous hydration. A recent report from the secondary analysis of RTOG 0617 suggested that the use of IMRT could lead to improved quality of life (QOL) without compromising patient survival (58). Taken together, IMRT do not compromise the treatment outcomes, including survival, toxicity and patients' QOL in lung cancer patients as compared with 3D-CRT, although its use for lung cancer remains somewhat controversial because of concerns about potentially inferior cancer outcomes related to interplay effects and potentially increased toxicity caused by larger volumes of normal tissue being exposed to low-dose radiation.

There were several small studies reported the clinical outcomes of using HT in NSCLC. In a prospective study (59), 40 consecutive stage III NSCLC patients were treated according to a uniform class solution (70.5 Gy in 30 fractions) with fixed constraints and priorities using HT. Acute grade 3 lung toxicity was seen in 10% of patients, and 16% maximally grade 3 late toxicity (lung toxicity exclusively) was observed after. Despite two deaths within 90 days after the start of RT from pulmonary toxicity, the acute and late toxicity profile was mostly acceptable when the MLD was kept to <18 Gy and the V20 was kept to <32%. The local progression-free survival (PFS) was considered encouraging for this unselected population, with the 1-year local PFS 66% and 2-year local PFS 50%. Adkison *et al*. (60) conducted a risk-stratified dose-escalating study with hypofractionated RT using HT for inoperable NSCLC, 46 stage I-III (80% stage III) patients were included, with no > grade 2 pneumonitis and esophageal toxicities were observed when radiation dose was escalated to 80.5 Gy in 25 fractions, and the median survival of 18 months was promising. The toxicity profiles between the above two studies (59,60) might due to the patient selections and chemotherapy-using, and also suggested the importance of the suitable dose-constrains setting. A retrospective study (61) from Korea assessed the clinical outcomes and complications in 37 NSCLC patients, the findings that treatment-related pneumonitis ≥ grade 3 occurred in seven patients and four patients died of treatment-related death from pneumonitis seemed higher than the historical control. Only contralateral lung V5 was found to significantly predict lung toxicity in the multivariate analysis, suggesting the different dose parameters chosen for planning between HT and conventional might be necessary because of the different radiation delivery modes.

IMRT and HT-based SBRT

SBRT is a non-invasive treatment that can deliver a high dose of radiation in a few fractions to the neoplastic lesions, which has been shown to be an excellent treatment option for early-stage NSCLC when a BED of ≥100 Gy is delivered (6,62,63). Because of the concern that the interplay effects will be more pronounced when the radiation was given in few fractions using fixed-field IMRT, the use of IMRT-based SBRT in lung tumors

was considered somewhat questionable. However, Seco *et al*. (64) concluded that for most clinical cases, any non-negligible effects of IMRT dose delivery may be clinically irrelevant when multiple beams are used. A study by Rao *et al*. (65) using 4D dose calculation based on deformable image registration with the simulation of interplay between MLC sequences and target movement showed the interplay effects were small in most patients. The interplay effects were reported be subtle in HT delivery even in one fraction treatment as mentioned above, the application of HT-based SBRT in lung cancers has been raised interest, particularly for the centrally located lesions for which severe toxicities were reported to be associated with conventional SBRT use due to their close proximity to critical organs (66). Several dosimetric studies have demonstrated the feasibility and superiority of using HT-based SBRT in early-stage NSCLC (67-69), especially for the centrally located tumors. Some clinical studies (70-73) have shown the acceptable safety and efficacy of IMRT and HT-based SBRT in lung cancer, albeit only short-term follow-up is available. Considering the excellent outcomes of conventional SBRT treatment for early-stage NSCLC, to select suitable cases that may benefit from HT-based SBRT becomes an important issue. Chi *et al*. (74) performed a study to explore the dosimetric selection criteria for HT-based SBRT delivering 70 Gy in 10 fractions to avoid severe toxicity in the treatment of centrally located lung tumors when adequate target dose coverage is desired, and suggested the most ideal candidates for HT-based SABR should have GTV ≤3.78 cm, or 11.98 cc; PTV≤4.90 cm, or 34.43 cc; ≤2 separate adjacent structures immediately adjacent to the GTV, the minimum GTV to OAR distance of ≥0.45 cm, and the minimum PTV to OAR distance of ≥0.21 cm. The clinical decision need to be further investigated bases on randomized trials.

Impression

The introduction of IMRT and HT can add the freedom of dose painting for lung cancer. However, the enhancement of capability or freedom in one facet of machine performance is often accompanied by a diminished capability or restriction in another, so the various delivery systems may ultimately prove optimal for different patient conditions. Actually, the delivery systems are likely to be distinguished not just by the dose distributions they can deliver but also by other clinical relevant factors. Given that IMRT and HT are more resource-intensive than conventional RT, and also considering the potential disadvantages of IMRT and HT, identifying patients who can particularly benefit from these advanced approaches need further investigation. Anyway, the clinical use of suitable radiation techniques should be finally decided on the basis on solitary clinical data. Besides the advances of radiation techniques, combination with systemic therapy is another way to improve treatment outcomes of lung cancer. Chemotherapy has been shown to increase the survival of lung cancer patients. Another systemic therapy evolving to target therapy specific to molecular abnormalities has been shown to yield better survival and less toxicity in selected cases. More research is needed combining targeted agents with RT. We also need a great understanding of the molecular events that take place in irradiated cells so that targeted agents can designed specifically to improve the therapeutic index of radiation.

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