International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

Intensity-Modulated Radiation Therapy in Locally Advanced Non-small Cell Lung Cancer

Aya Gawad Abou Al-Fetouh Mohamed Hussien[1*], Lobna Abdelaziz Abdelaziz[2], Ehab Mohamed Khalil[3], Doaa Abd El-Hady Hassan[2]

1 Clinical Oncology Department, Al-Ahrar Teaching Hospital, General Organization for Teaching Hospitals and Institutes (GOTHI), Egypt

2 Clinical Oncology & Nuclear Medicine Department, Faculty of Medicine, Zagazig University, Egypt

3 Radiation Oncology & Nuclear Medicine Department, NCI, Cairo University, Egypt

***Corresponding author:** Aya Gawad Abou Al-Fetouh Mohamed Hussien

Email: aya.arebelliousangel@gmail.com,

Abstract:

Intensity-modulated radiation therapy (IMRT) has become a standard radiotherapy technique in the management of lung cancer due to its ability to deliver highly conformal dose distributions while sparing surrounding normal tissues. By modulating beam intensity and utilizing advanced planning algorithms, IMRT allows improved target coverage, reduced radiation-induced toxicity, and the potential for dose escalation compared with conventional three-dimensional conformal radiotherapy. The integration of inverse planning, image guidance and functional imaging of motion management has further enhanced treatment precision and clinical outcomes. Despite these advantages, IMRT remains technically demanding and requires meticulous quality assurance to ensure safe and effective delivery. This review highlights the principles, planning techniques, delivery methods, clinical applications, and current evidence supporting the role of IMRT in lung cancer treatment.

Keywords: Intensity-modulated radiation therapy; IMRT; Lung cancer; Radiotherapy planning; Dose conformity; Toxicity reduction; Image-guided radiotherapy

Introduction:

Intensity-modulated radiation therapy (IMRT) now represents a standard technique used in treatment of lung cancer. It allows for improved 'shaping' of radiation dose profiles around tumor and at-risk nodal structures while sparing adjacent normal tissue structures. This capacity for improved dose distribution affords considerable opportunity to reduce the overall toxicity profile associated with radiation therapy **(1).**

Despite considerable promise, IMRT use remains in relatively early stages, and must be delivered with strict attention to organ motion and quality assurance as the clinical data and patient follow-up mature. Furthermore, IMRT is quite labour-intensive, with strong dependence on physics and quality assurance support, thus leaving open the possibility for significant heterogeneity in the precision of IMRT practice **(2).**

Intensity-modulated radiation therapy refers to a specific technique of linear accelerator-based radiation therapy whereby beams are modulated in such a manner to produce highly conformal dose distributions **(3).**

A primary objective of IMRT is to reduce dose to selected normal tissue structures in an effort to preserve function, while maintaining full dose delivery to tumor targets **(3).**

In contrast, IMRT is delivered by individually modulated fields (step and shoot or sliding window technique) or by a rotating linear accelerator gantry. Variable dose intensities can be delivered through the segments of each treatment field, thereby maximizing conformality of the ultimate dose distribution **(4).**

Advantages of IMRT in locally advanced NSCLC: (5)

- Improved target conformity, particularly for concave target volumes
- Can produce intentional dose inhomogeneity—dose-painting
- Increases normal tissue sparing
- Enables dose escalation
- Can compensate for missing tissue.

Disadvantages of IMRT: (6)

- Increased clinician time for target and organ outlining
- Needs extensive quality assurance programme
- Increased machine treatment time
- Increased planning time (initially)

IMRT planning:

- **Forward planning:**

IMRT plans were created by using the field-in-field (or forward-planned [FP] IMRT) technique. In which radiation oncologists designate targets (gross tumor, elective nodal regions) and avoidance structures (spinal cord, heart, etc.) then beam arrangement are used with generous field margins to account for daily set-up variation and physical characteristics of the beam itself. The radiation dose and profile is then calculated **(1).**

- **Inverse planning:**

One of the key features that distinguishes IMRT from other radiotherapy techniques is the use of computerised inverse planning. Conformal radiotherapy is forward planned and reliant on the skills of the treatment planner to decide the number, shape and orientation of the beams. Inverse planning, in contrast, specifies the plan outcome in terms of the tumor dose and normal structure dose limits. The computer system then adjusts the beam intensities to find a configuration best matched to the desired plan **(4).**

Each beamlet is traced through the patient producing an initial dose distribution. A small change is then made in the weighting of a single beamlet and this alteration is accepted if it results in an improved distribution **(7).**

This process is repeated for all beamlets during a single cycle (iteration) and should result in an improved plan. The iterative process is repeated for many cycles until no further improvement is seen. This results in the optimal intensity across each beam to produce the specified dose distribution. The calculations in this process would be impossible with a forward planned manual technique **(7).**

Currently, this planning process may be lengthy because the adjustments required to produce acceptable plans are not intuitive. With experience, total planning times are likely to be significantly reduced as centres develop standard field arrangements for use in particular tumor sites **(8).**

IMRT treatment delivery:

A number of diverse techniques have been developed to deliver IMRT. The two most common methods of segmental IMRT and dynamic IMRT use multi-leaf collimators (MLC) **(9).**

- **Static MLC:**

This method has evolved directly from conformal radiotherapy. For each beam orientation, several different MLC-shaped fields (segments) are created. A modulated field intensity is achieved by summing all the segments. The radiation is only turned on when the segments are in position and thus this method is known as step-and-shoot. This is now available from most linear accelerator manufacturers and is likely to become the most widely implemented technique **(9).**

- **Dynamic MLC:**

In contrast, with dynamic MLC-IMRT the MLC leaves are in continuous motion during treatment of each field. At a fixed beam angle, each pair of opposing MLC leaves is swept across the target volume under computer control to produce the desired fluence profile **(3).**

Variation of the speed and distance between leaves delivers the desired intensity of radiation to the specified point. This can produce more conformal dose distributions than segmental IMRT and is therefore more desirable for complex problems. This method does continue to deliver radiation while the MLC is in the beam, producing more leakage and increasing the total body dose **(3).**

- **Hyprid IMRT:**

Hybrid approach, combining the two techniques with the aim to create a more optimised dosimetric outcome. It combines static and IMRT beams treated concurrently. This technique was originally introduced as a method for the treatment of breast cancer. It consists of delivering the majority (approximately two thirds) of the prescribed dose with static beams and using IMRT beams to deliver the remainder **(10).**

Imaging and IMRT:

Tumor localization:

Accurate identification of the tumor is important for all radiotherapy techniques, but becomes even more essential with IMRT as the irradiated volume becomes so closely aligned to the target volume. CT scanning is the standard imaging modality for radiotherapy planning. It is widely available, geometrically accurate and provides electron density information that is necessary for planning algorithms. The main limitation of CT is that it cannot always identify the tumor adequately and other imaging modalities are needed to provide additional information **(5).**

Functional imaging techniques such as PET, SPECT and MRS are also potential tools for treatment planning, providing valuable information about patient and tumor physiology rather than anatomy. PET can be used with different tracers to assess microscopic nodal involvement and to define hypoxic or significantly proliferative areas within the tumor that could require boosting. However, these modalities have poor spatial resolution and need to be combined with CT imaging for radiotherapy planning **(6).**

Image fusion:

Image registration and fusion are techniques used to aid tumor localisation. Different imaging modalities are superimposed using internal landmarks or by matching on a voxel to voxel basis. This is used most frequently for

head and neck and brain tumors. Although clearly visible on MRI, the full extent of the tumor is usually not seen on the CT scan. The tumor contour drawn on the MRI is automatically transferred onto the corresponding CT image. This method allows the use of all relevant modalities to define the tumor, and the CT images can still be used for accurate planning calculations **(7).**

Image guidance:

Motion of the tumor between daily fractions is significant for many tumor sites and could result in a geographical miss. IGRT involves the incorporation of imaging before and/or during treatment to enable more precise verification of treatment delivery and allow for adaptive strategies to improve the accuracy of treatment. The main drawback of IGRT is the requirement for more time on the treatment couch and an increase in the total amount of radiation to the patient, especially with daily IGRT imaging schedules **(11).**

Image guidance can improve geometrical accuracy by adjusting the fields to the daily position of the target. Radiographic imaging of implanted radio-opaque markers is now feasible with electronic portal imaging **(1).**

A promising approach is the development of the cone-beam CT linear accelerator. A kilovoltage imaging system is integrated into the linear accelerator. A tomographic reconstruction of the volume is performed before treatment, and correction can be made for both target position and the set-up error. At present, routine use is not practicable due to the prolonged machine time required, but several centres are using this for research purposes **(12).**

Clinical implications:

Dose prescription-simultaneous modulated accelerated RT:

The clinician must specify the required dose to be delivered to the target volume and also define the dose limits for the organs at risk. With conventional and conformal treatments, tumors in close proximity to radiosensitive structures often require very complex treatment plans. The dose to the tumour may need to be reduced to prevent unacceptable late complications **(12).**

Frequently, it is necessary to divide the treatment course into several phases, each of which has different field arrangements. IMRT allows the allocation of different dose targets for treatment (‘dose-painting’) creating an intentionally inhomogeneous dose distribution. It is possible to simultaneously boost the areas of higher risk allowing the patient to be treated in a single phase. This technique of simultaneous modulated accelerated RT (SMART) is very efficient to plan and deliver, can escalate the tumor dose and will decrease total treatment time **(12).**

Clinical research efforts in IMRT have generally considered two basic paradigms. The first research strategy seeks to maintain current tumor control rates while decreasing toxicity profiles. For example, IMRT studies in H&N cancer commonly strive to maintain conventional dose to primary tumor and at-risk nodal regions, while diminishing dose to adjacent normal tissue structures such as salivary glands and spinal cord **(6).**

The second strategy attempts to escalate tumour target dose while maintaining acceptable levels of toxicity. This approach has been taken in dose-escalation and hypofractionation trials for prostate cancer and more recently in lung cancer **(6).**

Effectiveness of IMRT:

- ✓ **In local control and overall survival:**

IMRT has emerged as an effective treatment for locally advanced lung cancer. Previously, the clinical outcomes of unresectable locally advanced lung cancer were poor, and the median survival time of patients treated with radiotherapy alone was only 12 months **(13).**

There have been some randomized prospective trials comparing the survival outcomes of IMRT and 3D-CRT in the treatment of non-small cell lung cancer. Previous studies using the US SEER-Medicare data did not find significant differences in survival outcomes between IMRT and 3D-CRT **(5).**

Shirvani et al. investigated predictors of IMRT use in the United States between 2001 and 2007, using the Surveillance, Epidemiology, and End Results (SEER) Medicare database. They reported that the year of diagnosis and treatment in a dedicated radiotherapy center were the only independent predictors of IMRT use. Lung and esophageal toxicity was equal between the IMRT and 3DCRT groups **(5).**

A further population-based study using the SEER database compared treatment outcomes in stage III NSCLC for IMRT, 3DCRT, and two-dimensional radiotherapy (2DRT) planning techniques. It was conducted to evaluate IMRT inaccuracies in dose and increased long-term toxicity, which in turn could affect survival. This analysis of nearly 7000 patients confirmed that IMRT was associated with similar toxicities and OS to 3DCRT, with both techniques showing an advantage over 2DRT **(5).**

A meta-analysis study also reported no significant survival differences. However, several single institution studies have reported that IMRT significantly improved the overall survival compared with 3D-CRT in the treatment of non-small cell lung cancer, Liao et al retrospectively analyzed the treatment outcomes of 496 patients with non-small cell lung cancer who were treated with either IMRT or 3D-CRT and reported that overall survival was significantly better in patients treated with IMRT. McCloskey et al also reported significantly better overall survival outcomes in patients treated with IMRT in their retrospective single institution study **(14).**

To compare the survival rates of patients with stage III non-small cell lung cancer who were treated with either 3D-CRT or IMRT, a study was done from January 2008 to July 2015, 19 patients were treated with IMRT and 30 were treated with 3D-CRT, The 1- and 2-year overall survival rates were 94.7% and 77.1% in the IMRT group and 76.7% and 52.5% in the 3D-CRT group, respectively **(8).**

The overall survival rates of the IMRT group were higher than those of the 3D-CRT group; however, these differences were not statistically significant (P=0.072). Gross tumor volume was significantly associated with the overall survival rate. The 1- and 2-year loco-regional recurrence-free survival rates were 63.2% and 51% in the IMRT group and 67.5% and 48.1% in the 3D-CRT group (P=0.897), respectively. The 1- and 2-year distant metastasis-free survival rates were 78.9% and 68.4% in the IMRT group and 62.6% and 40.9% in the 3D-CRT group (P=0.120), respectively **(8).**

- ✓ **In dose escalation:**

Conventional radiotherapy using 60 Gy in 30 fractions combined with chemotherapy has been the standard regimen for unresectable NSCLC. Several studies on radiation dose escalation have been conducted to improve LC **(15).**

A potential advantage of IMRT over 3DCRT is the ability to safely escalate radiotherapy dose. One of the first studies to address this issue was a phase I dose escalation study (84 Gy/35 fractions) of IMRT in stage III NSCLC and induction chemotherapy. This study was halted after the enrolment of five patients as one patient died of pneumonitis. This may have been due to an adverse effect of chemotherapy on baseline lung function or the hypofractionated dose regime; however, this study has been criticized for using an inadequate dose calculation algorithm, leading to systematic underestimation of doses to the tumor and organs at risk **(8).**

The NRG Oncology RTOG 0617 study enrolled 482 patients with locally advanced NSCLC from 2007 to 2011 and compared a high dose of radiation (74 Gy) with a standard dose (60 Gy). All patients were treated with concurrent chemotherapy (carboplatin or paclitaxel with or without cetuximab). Of these patients, 47% were treated with IMRT and 53% with 3D-CRT. The secondary analysis was based on a median follow-up of 5.2 years. Surprisingly, at interim analysis the data suggested a survival disadvantage for the high-dose arm as well as inferior

local control rates, indicating that dose escalation using conventional fractionation (resulting in increased overall treatment time) is not the ideal approach for NSCLC. Although patients were stratified by treatment delivery technique and the proportions of patients treated with IMRT were balanced between treatment groups (46.1% in 60 Gy arms and 47.1% in 74 Gy arms), the delivery of 74 Gy was probably challenging, particularly in patients treated without IMRT, given the gross tumor volume (GTV) (mean 124.7 in 60 Gy arms and 128.5 cc in 74 Gy arms) **(7).**

Despite the similarity in outcomes between the two techniques, IMRT demonstrated a clear advantage in reducing the risk of lung toxicity over the longer term. The rate of pneumonitis at a median follow-up of 5.2 years was 3.5% vs 8.2%, respectively, for IMRT vs 3D-CRT (P = .03) **(7).**

A subsequent analysis on patient reported outcome demonstrated a significantly worse quality of life on the 74 Gy arms at 3 months after treatment. Interestingly, the decline in quality of life was significantly reduced with the use of IMRT compared to 3DCRT suggesting that the use of improved radiotherapy treatment techniques may be beneficial **(7).**

More recently, results of a phase I trial of hypofractionated, dose escalating IMRT in NSCLC were published, Seventy-nine patients received dose escalated treatments based on the patients' stratified risk for TRP in 25 daily fractions. Patients with all stages of disease were recruited and 62% received chemotherapy in the neoadjuvant or adjuvant setting. Patients were all positron emission tomography staged, planned using four-dimensional (4D) CT and the treatment was delivered with helical tomotherapy **(5).**

The dose was prescribed such that 95% of the PTV volume received the prescription dose. Despite escalation to doses of up to 85.5 Gy/25 fractions, no grade 3 acute or late esophageal toxicity and no grade 3 pneumonitis was seen; however, six grade 4/5 toxicities were encountered in the form of massive hemoptysis and bronchocavitary fistula. Both these toxicities were associated with centrally based tumors, doses above 75 Gy, and specific 1–3 cc doses to the proximal bronchial tree **(5).**

No constraints for proximal bronchial tree were specified in the trial protocol. After a median follow-up of 17 months median survival was 16 months and 3-year OS was 29%, which does not appear superior to historical outcome **(5).**

The largest body of evidence for IMRT in locally advanced NSCLC originates from three retrospective publications of patient cohorts from the same cancer center (MD Anderson Cancer Centre, Texas). It should be emphasized that as the treatment groups were not fully balanced and positron emission tomography staging was introduced at the time of recruitment to the IMRT cohorts, the data need to be interpreted with caution. Nevertheless, these studies all suggested improved outcomes with IMRT, reporting less toxicity and a superior OS **(5).**

Yom et al. evaluated the rate of TRP in 68 NSCLC patients (85% stage III) treated with IMRT between 2002 and 2005, and compared this to a group of 222 historical controls treated with 3DCRT (2000–2003). Reasons for implementing IMRT included large treatment volume, failure to meet normal tissue dose constraints for 3DCRT, synchronous lung primary tumors, and poor baseline pulmonary function. In both groups, the majority of patients received a treatment dose of 63 Gy in 35 fractions and concurrent platinum-based doublet chemotherapy. Despite a larger GTV in the IMRT group (194 versus 142 cc), patients achieved significantly lower volumes of lung receiving 20 Gy (V20), however had larger volumes of lung receiving 5 Gy (V5) compared to the 3DCRT group. With a median follow-up of eight (0–27) and nine (0–56) months, respectively, the incidence of greater than grade 3 TRP was significantly lower in the IMRT group than in those treated with 3DCRT (8% versus 22% at 6 months). Local control in the IMRT group at 12 months was 55.3% with an estimated OS at 12 months of 57% **(5).**

- ✓ **In decreasing toxicity:**

In a secondary analysis of the RTOG 0617 trial, IMRT was compared with conventional three-dimensional conformal radiation therapy (3D-CRT). Despite a significantly higher planned target volume in the IMRT group than

in the 3D-CRT group, the incidence of ≥ grade 3 radiation pneumonitis in the IMRT group was significantly lower (3.5% vs 7.9%, P = 0.039) **(8).**

IMRT significantly reduced heart V40 compared to 3D-CRT (16.5% vs 20.5%; P < .001). Heart V40 (<20%) had better OS than V40 (≥20%. Based on these results, this study supports the routine use of IMRT for locally advanced NSCLC, which has led to further adoption of IMRT in clinical situations **(8).**

IMRT can reduce V20Gy compared with 3D-CRT, which is considered a major factor in reducing the risk of radiation pneumonitis with IMRT. In contrast, IMRT tends to have a wider low-dose distribution than 3D-CRT because of its characteristic of delivering irradiation from more diverse angles than 3D-CRT. There are various reports on the potential for low-dose ranges to spread to the lungs and cause severe radiation pneumonitis, and the percentage of lung volume that received ≥ 5 Gy (V5Gy) has been the most studied factor. A multi-center retrospective study in Japan examined risk factors for ≥ grade 2 radiation pneumonitis and found V5Gy to be an important parameter, concluding that V5Gy < 60% is recommended **(6).**

IMRT planning generally decreases the medium-dose range, such as V20Gy, and increases the low-dose range, such as V5Gy. Planners should be aware of this point and plan IMRT carefully so as not to focus excessively on one parameter at the expense of others. One way to consider this balance is to plan a simulated 3D-CRT and validate that the IMRT plan is superior to the simulated 3D-CRT plan. The treatment planning goals of increasing V5Gy to acceptable levels and decreasing V20Gy compared with that in 3D-CRT are simple and help ensure the quality of IMRT planning **(13).**

Elective radiotherapy of the mediastinum has been the standard for stage III lung cancer; however, involved-field radiotherapy, which omits elective radiotherapy, is being considered to reduce adverse events and improve prognosis. A pooled analysis of several studies for stage III NSCLC showed that the involved-field radiotherapy group had a significantly better OS than the elective radiotherapy group **(13).**

Recently, cardiac radiation dose has been reported to be associated with mortality risk, and this area has received increasing attention. IMRT can reduce not only the lung dose but also the cardiac dose compared to 3D-CRT; Speirs et al. concluded that IMRT is associated with a significantly lower cardiac dose than 3D-CRT and is associated with cardiotoxic events and prognostic factors. Although no firm conclusions on specific dose-volume parameters or high-risk cardiac exposure sites have been reached, and further data analysis is still needed, it is also important to reduce the cardiac dose as much as possible and avoid radiation-induced cardiotoxicity, which strengthens the rationale for the adoption of IMRT **(16)**

In conclusion, recent developments in IMRT for lung cancer have been described, and the adoption and quality improvement of IMRT remain topics of interest. Radiation oncologists should improve their skills in planning IMRT and continue researching the treatment outcomes of IMRT **(13).**

Their most recent study assessed long-term clinical outcome of patients treated with 4DCT IMRT (n = 165; 76% stage III) with or without concurrent chemotherapy. The median radiation dose was 66 Gy given in 33 fractions and median GTV was 124.6 cc (range, 4.3–730 cc). Eleven percent of patients developed greater than or equal to grade 3 TRP at 6 months and one patient was affected by grade 3 pulmonary fibrosis at 18 months **(5).**

The majority of the 29 patients (18%), who experienced grade 3 esophagitis settled within 6 weeks, however four went on to develop an esophageal stricture requiring further intervention. Overall, the incidence and severity of toxicities were lower in IMRT patients than historical control cohorts who received 3DCRT. With a median 16.5 months follow-up, 2-year disease free and OS were 38% and 46%, respectively **(5).**

✓ **With PET:**

^{18}F-FDG PET-based planning could potentially improve local control and does not seem to increase toxicity in patients with chemoradiotherapy-treated locally advanced non-small-cell lung cancer. Imaging-based target volume reduction in this setting is, therefore, feasible, and could potentially be considered standard of care. The procedures established might also support imaging-based target volume reduction concepts for other tumours **(17).**

An FDG-PET-based randomized study showed that the risk of locoregional progression in the involved-field radiotherapy group was non-inferior to that in the elective radiotherapy group. These findings suggested that involved-field radiotherapy based with FDG-PET is a promising treatment option for stage III NSCLC **(17).**

In the REPAINT trial which is a randomized trial, Metabolic tumor volume for each pulmonary tumor and involved lymph node was calculated using fludeoxyglucose PET. Participants were randomly assigned 1:1 to receive standard RT (60 Gy in 30 fractions delivered to pulmonary tumors and involved lymph nodes) versus dose-painted RT (55 Gy delivered to tumors and lymph nodes with metabolic volume exceeding 20 cm^3 and 44-48 Gy to other lesions, all in 20 fractions). Concurrent chemotherapy and standard adjuvant therapy were given in both arms. The primary objective was to characterize patient-reported outcomes using Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events. Secondary objectives included comparing outcomes between study arms. Fifty patients were enrolled. The most common grade 3 patient-reported adverse events within 90 days of RT completion were dysphagia (38%), fatigue (38%), cough (32%), and wheezing (28%) **(18).**

The median progression-free survival duration was 18 months, and the median overall survival duration was 42 months. Progression-free survival and overall survival rates were similar across study arms (logrank P = .562 and .765, respectively). There have been 3 cases of in-field disease progression, with 1 in the control arm and 2 in the dose-painted arm. Grade 3-4 lymphopenia was reduced with dose-painted RT (48% vs 81%, chi-square P = .012), so it found that PET-adjusted, dose-painted IMRT for locally advanced non-small cell lung cancer is feasible and does not compromise clinical outcomes compared to standard radiotherapy. This risk-adapted approach reduced normal tissue irradiation and treatment-associated lymphopenia while maintaining high-quality disease control **(18).**

References:

1. Ng, W. T., Soong, Y. L., Ahn, Y. C., AlHussain, H., Choi, H. C., Corry, J., ... & Lee, A. W. (2021). International recommendations on reirradiation by intensity modulated radiation therapy for locally recurrent nasopharyngeal carcinoma. International Journal of Radiation Oncology* Biology* Physics, 110(3), 682-695
2. Das, I. J., Sanfilippo, N. J., Fogliata, A., & Cozzi, L. (2020). Intensity modulated radiation therapy: a clinical overview. IOP Publishing.
3. DeWees, T. A., Voss, M. M., Breen, W. G., Chiang, J. S., Ding, J. X., Daniels, T. B., ... & Sio, T. T. (2022). Cardiopulmonary toxicity following intensity-modulated proton therapy (IMPT) versus intensity-modulated radiation therapy (IMRT) for stage III non-small cell lung cancer. Clinical lung cancer, 23(8), e526-e535.
4. Haslett, K., Bayman, N., Franks, K., Groom, N., Harden, S. V., Harris, C., ... & Faivre-Finn, C. (2021). Isotoxic intensity modulated radiation therapy in stage III non-small cell lung cancer: a feasibility study. International Journal of Radiation Oncology* Biology* Physics, 109(5), 1341-1348.
5. Chan, C., Lang, S., Rowbottom, C., Guckenberger, M., Faivre-Finn, C., & IASLC Advanced Radiation Technology Committee (2014). Intensity-modulated radiotherapy for lung cancer: current status and future developments. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer, 9(11), 1598–1608. https://doi.org/10.1097/JTO.0000000000000346
6. Tsukita, Y., Yamamoto, T., Mayahara, H., Hata, A., Takeda, Y., Nakayama, H., ... & Sugiura, H. (2021). Intensity-modulated radiation therapy with concurrent chemotherapy followed by durvalumab for stage III non-small cell lung cancer: A multi-center retrospective study. Radiotherapy and Oncology, 160, 266-272.

7. Chun SG, Hu C, Choy H, et al: Long-term outcomes by radiation technique for locally advanced non-small lung cancer: A secondary analysis of NRG Oncology-RTOG 0617 at 5 years. 2023 World Conference on Lung Cancer. Abstract OA17-04. Presented September 11, 2023.
8. Chun, S. G., Hu, C., Komaki, R. U., Timmerman, R. D., Schild, S. E., Bogart, J. A., ... & Bradley, J. D. (2024). Long-term prospective outcomes of intensity modulated radiotherapy for locally advanced lung cancer: a secondary analysis of a randomized clinical trial. JAMA oncology, 10(8), 1111-1115.
9. Liu, J., Li, T., Xiaohu, W., Su, S., Li, Q., Geng, Y., ... & Lu, B. (2021). The therapeutic value of volumetric-modulated arc therapy in advanced non-small cell lung cancer primary tumors: a multicenter retrospective analysis based on propensity score matching and comparison with intensity-modulated radiotherapy.
10. Bi, S., Zhu, R., & Dai, Z. (2022). Dosimetric and radiobiological comparison of simultaneous integrated boost radiotherapy for early stage right side breast cancer between three techniques: IMRT, hybrid IMRT and hybrid VMAT. Radiation oncology (London, England), 17(1), 60. https://doi.org/10.1186/s13014-022-02009-2
11. Grégoire, V., Guckenberger, M., Haustermans, K., Lagendijk, J. J. W., Ménard, C., Pötter, R., Slotman, B. J., Tanderup, K., Thorwarth, D., van Herk, M., & Zips, D. (2020). Image guidance in radiation therapy for better cure of cancer. Molecular oncology, 14(7), 1470–1491. https://doi.org/ 10.1002/1878-0261.12751
12. Muster, J., Alt, N. J., Edelmann, M., Anczykowski, M. Z., Zwerenz, C. M., Schirmer, M. A., ... & Dröge, L. H. (2025). Treatment of non-small cell lung cancer: advances following the introduction of PET-CT and IMRT/VMAT. Strahlentherapie und Onkologie, 1-14.
13. Shirai, K., Aoki, S., Endo, M., Takahashi, Y., Fukuda, Y., Akahane, K., Musha, A., Sato, H., Wakatsuki, M., Ishikawa, H., & Sasaki, R. (2025). Recent developments in the field of radiotherapy for the management of lung cancer. Japanese journal of radiology, 43(2), 186–199. https://doi.org/ 10.1007/ s11604-024-01663-8
14. Allen, S. G., Schonewolf, C. A., Schipper, M. J., Yin, H. M., Paximadis, P. A., Kestin, L. L., Dominello, M., Wilson, M., Matuszak, M. M., Hayman, J. A., & Jolly, S. (2025). Dosimetry and Toxicity Comparison of Three-Dimensional Conformal Radiation Therapy and Intensity Modulated Radiation Therapy in Locally Advanced Lung Cancer Across a Large Statewide Quality Collaborative. International journal of radiation oncology, biology, physics, 122(5), 1248–1256. https://doi.org/10.1016/j.ijrobp.2025.03.007
15. Kong, F. S., Hu, C., Pryma, D. A., Duan, F., Matuszak, M., Xiao, Y., Ten Haken, R., Siegel, M. J., Hanna, L., Curran, W. J., Dunphy, M., Gelblum, D., Piert, M., Jolly, S., Robinson, C. G., Quon, A., Loo, B. W., Srinivas, S., Videtic, G. M., Faria, S. L., … Machtay, M. (2024). Primary Results of NRG-RTOG1106/ECOG-ACRIN 6697: A Randomized Phase II Trial of Individualized Adaptive (chemo)Radiotherapy Using Midtreatment 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Stage III Non-Small Cell Lung Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 42(33), 3935–3946. https://doi.org/10.1200/JCO.24.00022
16. Vojtíšek R. (2020). Cardiac toxicity of lung cancer radiotherapy. Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology, 25(1), 13–19. https://doi.org/ 10.1016/ j.rpor.2019.10.007
17. Nestle, U., Schimek-Jasch, T., Kremp, S., Schaefer-Schuler, A., Mix, M., Küsters, A., Tosch, M., Hehr, T., Eschmann, S. M., Bultel, Y. P., Hass, P., Fleckenstein, J., Thieme, A., Stockinger, M., Dieckmann, K., Miederer, M., Holl, G., Rischke, H. C., Gkika, E., Adebahr, S., … PET-Plan study group (2020). Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial. The Lancet. Oncology, 21(4), 581–592. https://doi.org/10.1016/S1470-2045(20)30013-9
18. Ohri, N., Bodner, W. R., Kabarriti, R., Shankar, V., Gucalp, R., Cheng, H., & Halmos, B. (2025). Randomized Evaluation of the PET-Adjusted IMRT for NSCLC Trial (REPAINT). International journal of radiation oncology, biology, physics, 122(2), 365–373. https://doi.org/10.1016/j.ijrobp.2025.01.005