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Original Research Article

Efficacy and Toxicity of Moderately Hypo fractionated Radiation Therapy with Helical TomoTherapy Versus Conventional Radiation Therapy in Patients with Unresectable Stage III Non-Small Cell Lung Cancer Receiving Concurrent Chemotherapy

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Abstract:

Background: The conventional treatment regimen for inoperable stage III non-small cell lung cancer (NSCLC) involves the administration of chemotherapy and radiation therapy (60 Gy administered in 30 fractions). However, moderately hypofractionated radiation therapy (Hypo-RT) has also been explored as a potential alternative approach.

Aim and Objectives: The objective of this study was to assess the effectiveness and toxicity of moderately Hypo-RT with helical TomoTherapy compared to conventionally fractionated radiation treatment (Con-RT) in patients with unresectable stage III NSCLC who are also undergoing concomitant chemotherapy.

Methods and Materials: The research randomly assigned eligible patients to either the Hypo-RT group (receiving 60 Gy in 20 fractions) or the Con-RT group (receiving 60 Gy in 30 fractions) at a ratio of 1:1. Each patient had two cycles of simultaneous platinum-based chemotherapy followed by two cycles of consolidation treatment. The main objective was to assess the overall survival (OS) at the 3-year mark in the intention-to-treat population. The secondary outcomes measured in this study were progression-free survival and treatment-related adverse events.

Results: There were a total of 146 patients that participated in the study. The duration of observation was 46 months, with the median value being used as a representative measure. The 3-year overall survival rates in the Hypo-RT and Con-RT groups were 58.4% and 38.4%, respectively. The difference between the two groups was statistically significant (P = 0.021). The median overall survival (OS) from randomization was 41 months in the Hypo-RT group and 30 months in the Con-RT group. The difference between the two groups was statistically significant, with a p-value of 0.021. There was no notable disparity in the frequencies of grade ≥2 treatment-related adverse events between the two groups.

Conclusions: Utilizing helical TomoTherapy with a moderately Hypo-RT approach may enhance overall survival (OS) in individuals diagnosed with unresectable stage III NSCLC, while simultaneously keeping toxicity rates at a manageable level.

Keywords: Chemotherapy; Lung cancer; Radiation therapy.

Introduction

The recommended approach for treating inoperable stage III non-small cell lung cancer (NSCLC) is the simultaneous or sequential administration of chemotherapy and radiation therapy (RT) using conventional fractionation of 60 Gy delivered in 30 fractions. [1,2] Nevertheless, research indicates that non-small cell lung cancer (NSCLC) cells exhibit fast growth and often start to reproduce at an increased rate between weeks 3 and 4 after radiation therapy (RT), resulting in an unfavourable prognosis. [3,4] The 3-year overall survival (OS) rate ranges from 18.1% to 23.8%. [1] Consequently, recent efforts have concentrated on enhancing the efficiency of RT to enhance locoregional control (LRC) and overall survival (OS). This has been achieved by radiation dosage

escalation, as assessed in Radiation Therapy Oncology Group 0617, [2], and the use of new RT methods, as reviewed in NCT00915005. [5] Nevertheless, both of these experiments failed to yield enhanced results. Nevertheless, the PACIFIC study revealed that patients who were administered durvalumab had a 5-year progression-free survival (PFS) rate of 33.1%. Additionally, the majority of patients encountered intrathoracic failure as their initial progression. [6,7]

This highlights the possibility for additional enhancement of local control rates. In order to achieve this goal, some studies have suggested increasing the daily radiation dosage while shortening the total treatment period. This is done to administer a greater biologically effective dose (BED) to the tumour, which helps to restrict the growth of tumour cells and enhance survival rates. [8-11]

Nevertheless, because to the larger portion size in hypofractionated RT (Hypo-RT), it is crucial to ensure the accuracy of RT administration in order to safeguard organs at risk (OARs) such as the oesophagus, lungs, tracheobronchus, and heart. Helical TomoTherapy (HT) is a device that uses image guidance to administer intensity modulated radiation therapy (IMRT). It does this by combining a fan-beam that rotates constantly with synchronised movement of the treatment couch. [12-17]

In a prior retrospective analysis, we documented the safety and effectiveness of hypofractionated radiotherapy guided by hypoxia imaging in patients diagnosed with inoperable stage III non-small cell lung cancer. [16]

Aim and objectives:

This study aimed to assess the effectiveness and safety of Hypo-RT, which involved delivering 60 Gy in 20 fractions using HT, compared to conventionally fractionated RT (Con-RT), which provided 60 Gy in 30 parts. The study focused on patients with unresectable stage III NSCLC who were also undergoing concurrent chemotherapy (CCT). The study sought to examine if the utilization of sophisticated RT methods in conjunction with optimized segmentation patterns results in improved clinical outcomes.

Material and methods:

Study design: This research recruited patients with histologically confirmed unresectable stage III NSCLC at a medical college facility in central India. Patients who had experienced weight loss of less than 10% in the month prior were considered suitable. Patients deemed unsuitable for concomitant chemotherapy/RT following consultation with radiation oncology specialists and medical oncologists were deemed ineligible. Initial assessments consisted of advanced computed tomography (CT) scans of the chest and upper abdomen, magnetic resonance imaging (MRI) of the brain, a comprehensive blood cell analysis with differentiation, and evaluations of hepatic and renal function. Positron emission tomography (PET)-CT was suggested but not obligatory. The study obtained approval from the institutional ethics committee.

All patients participating in the trial provided written informed consent. Patients who met the criteria were randomized randomly in equal numbers to receive either considerably hypofractionated radiotherapy (60 Gy in 20 fractions) or conventionally fractionated radiotherapy (60 Gy in 30 fractions). Patients had radiotherapy (RT) treatment five days per week, from Monday to Friday, with radiation doses administered in fractions of 2 or 3 Gy. RT was administered using TomoTherapy with a 6 MV beam in the Hypo-RT group, while the Con-RT group received RT by IMRT with a range of 6-18 MV. There was no difference in the method used for contouring and defining margins between the groups.

The clinical target volume of the lymph nodes encompassed the full area of the affected lymph nodes as identified by CT or PET-CT. A buffer of 1.0 to 1.5 centimetres was employed around the planned goal volume to account for breathing motions and setup faults. All radiation therapy plans were created with the objective of achieving a dosage that covers 95% of the intended target volume. The target delineation and treatment planning were implemented according to the previously provided instructions. [16-18]

All patients had two cycles of neoadjuvant concurrent chemoradiotherapy (CCT), followed by two rounds of chemotherapy, which included a regimen consisting of a combination of two drugs, one of which was a platinum-based compound. The initial round of chemotherapy started on the first day after radiation therapy and was then repeated every 21 days. Participating institutions established radiographic standards and conducted regular talks within each institution to assure the quality of radiographic images.

Study endpoints:

The intention-to-treat population comprised all patients who were randomly allocated to one of the therapy groups. The main objective of the study was to assess the overall survival (OS) rate after 3 years. The secondary objectives included evaluating the progression-free survival (PFS) rate and monitoring any adverse events connected to the therapy. Time to event was defined as the duration between the randomization and the initial occurrence of the desired outcome. Overall survival

(OS) was defined as the period of time from the moment of random assignment to either death from any cause or the date of the final follow-up in patients whose data was incomplete. [19] Biopsies were conducted in instances when there was suspicion of progressing illness, but it had not been confirmed with imaging or PET-CT/CT scans.

LRC is the duration between randomization and the occurrence of locoregional failure (LRF). LRF was characterised as the reoccurrence of a disease in the chest, which was proven via imaging exams (such as CT or PET-CT) and/or positive histology/cytology. The possibility of cancer reappearing in another lobe of the lung, whether on the same side (ipsilateral) or the other side (contralateral), was not recognized as local recurrence of the disease. The diagnostic techniques employed in LRF diagnosis were identical to those utilized in the prior investigation. [21]

Statistical analysis: In this comparative randomized controlled trial (RCT), the anticipated three-year overall survival (OS) rate was 50% for patients who received Hypo-RT with HT, and 26% for those who received Con-RT. [16-22]

The overall survival (OS) and progression-free survival (PFS) rates were determined in the intention-to-treat population, commencing from the date of patient enrolment. The R statistical program (version 4.0.5) was used for all statistical analyses. The estimates for LRC, PFS, and OS were calculated using the Kaplan-Meier curve and then compared using the log-rank test. The statistical tests conducted were two-sided, and significance was determined by a P value of less than 0.05. The trial was overseen by the data monitoring committee of Zhongshan Hospital, and no prep lanned interim analyses were conducted. The statistical procedures adhered rigorously to the experimental design, with no alterations made subsequent to the commencement of the investigation.

Results

Table 1 displays the demographic and clinical characteristics of the group. The median ages of the Hypo-RT and Con-RT groups were 64 and 65 years, respectively. Both groups consisted mostly of male patients. The prevalence of patients having a prior diagnosis of chronic obstructive lung disease (as defined by the Global Initiative for Chronic Obstructive Lung Disease criteria [23]) was greater in the Hypo-RT group compared to the Con-RT group (21.9% vs 12.3%, P = 0.061). The pathological TNM stage and histological types were similar in both groups.

One patient from both the Hypo-RT and Con-RT groups did not finish the treatment because they did not comply well with receiving radiation therapy and chemotherapy at the same time. Out of the whole group, 6 patients (4.2%) got just 1 cycle of CCT instead of the intended 2 cycles. This was because they did not fully recover from haematologic toxicity during RT.

Specifically, 4 patients experienced grade 3/4 neutropenia, 1 patient had raised creatinine levels, and 1 patient had elevated transaminase levels. One patient from both the Hypo-RT and Con-RT groups ceased treatment due to noncompliance with the chemotherapy/radiotherapy regimen. Four patients from the Hypo-RT group and two patients from the Con-RT group had their treatment interrupted.

Table 1: Patient and tumor profile

Variables		Hypo-RT (n=73)	Con-RT (n=73)	P- Value
Age (years), median		64	65	0.861
		20 (24.1)	12 (14.5)	
		18 (21.7)	10 (12.0)	
Gender	Female	13 (17.8%)	13 (17.8%)	1.001
	Male	60 (82.2%)	60 (82.2%)	
Performance status	0	41 (56.2%)	50 (68.5%)	0.081
	1	30 (41.1%)	18 (24.7%)	
	2	02 (2.7%)	05 (6.9%)	
Habits	Non-Smoker	30 (41.1%)	35 (48.0%)	0.561
	<30 pack years	12 (16.4%)	11 (15.01%)	
	>30 pack years	31 (42.5%)	27 (37.0%)	
Histology	Squamous carcinoma	37 (50.7%)	34 (46.6%)	0.481
	Adenocarcinoma	26 (35.6%)	31 (42.5%)	
	Large cell undifferentiated	04 (5.5%)	05 (6.9%)	
	NSCLC NOS	06 (8.2%)	03 (4.1%)	
Mutation status	EGFR/ALK	13 (50.0%)	12 (38.7%)	0.431
	KRAS/MET/ROS1	02 (12.5%)	03 (9.7%)	0.991
	Negative	11 (42.3%)	16 (51.6%)	0.601
Tumor size (mm), median		37	44	0.111

The dosimetric parameters employed, and all treatment plans successfully adhered to the dosage limitations of the organs at risk (OAR). The physiologically effective doses, calculated using α/β ratios of 10Gy (BED10) [24], were 78 Gy for the Hypo-RT group and 72 Gy for the Con-RT group. The Hypo-RT group had a slightly higher bilateral lung V5 (49.6% vs 48.3%) compared to the Con-RT group. On the other hand, the Hypo-RT group had slightly lower bilateral lung V10, V20, and V30 compared to the Con-RT group. However, none of these changes were statistically significant. The average lung dose was marginally lower in the Con-RT group compared to the Hypo-RT group (P = 0.581), and the volume of the heart receiving 35 Gy (V35) was slightly, but not substantially, lower in the Hypo-RT group (P = 0.651). There were no notable disparities in GTV (P = 0.141) or planned goal volume (P = 0.691) across the groups.

Survival: The median follow-up for the entire group was 46 months, with a range of 10 to 58 months for live patients and 5 to 51 months for deceased patients. The median follow-up duration for both the Hypo-RT and Con-RT groups was 46 months, and there was no statistically significant difference between the two groups (P > 0.05). There were significant differences in the median and 3-year overall survival (OS) rates between the Hypo-RT and Con-RT groups. The median OS was 41 months for the Hypo-RT group and 30 months for the Con-RT group (P = 0.021). The median 3-year OS was 58.4% for the Hypo-RT group and 38.4% for the Con-RT group (P = 0.021). The median progression-free survival (PFS) was considerably enhanced in the Hypo-RT group compared to the Con-RT group, with a duration of 16 months against 10 months (P = 0.0031). The Hypo-RT group had a considerably longer time to median locoregional recurrence compared to the Con-RT group (not reached versus 25 months: P = 0.0021).

Response and failure patterns: The Hypo-RT group had a decreased risk of locoregional recurrence compared to the Con-RT group (P = 0.041) (Table 2). The Hypo-RT group had a decreased risk of distant recurrence compared to the Con-RT group, however this difference did not reach statistical significance (P = 0.311). (Table 2)

Table 2: Pattern of failure

Recurrence pattern	Hypo-RT	Con-RT	P- Value
Total	49 (67.1%)	58 (79.5%)	0.131
Local - regional failure	23 (31.5%)	36 (49.3%)	0.041
Distant failure	27 (37.0%)	34 (46.6%)	0.311

Toxicity: There was no significant difference between the two groups in terms of the occurrence of acute radiation pneumonia (RP) (P = 0.211), late RP (P = 0.14), and grade ≥2 radiation oesophagitis (P = 0.491). Two patients (2.7%) in the Hypo-RT group experienced grade 2 acute RP, whereas one patient (1.4%) experienced grade 3 acute RP. In the Con-RT group, three patients (4.1%) experienced grade 2 acute RP and four patients (5.5%) experienced grade 3 acute RP. Out of the patients in the Con-RT group, only one (1.4%) suffered severe grade 4 acute RP. However, none of the patients in the Hypo-RT group developed acute RP of grade 4 or above. Fatigue, chest discomfort, and skin toxicity were infrequent in both groups. (Table 4)

Discussion

Modestly hypofractionated radiation therapy (Hypo-RT) regimens, with or without concurrent chemotherapy (CCT), are being used more often as an alternative to conventional radiation therapy (Con-RT) for stage III inoperable non-small cell lung cancer (NSCLC). The effectiveness of Hypo-RT in patients with stage III inoperable NSCLC has been demonstrated. [25-28] In our prior retrospective investigation, we also found evidence supporting the effectiveness of Hypo-RT. Although showing promise, these results do not align with two previous investigations. [29, 30]

However, in those trials, patients were administered contemporaneous or sequential chemotherapy in varying amounts. Furthermore, variations in clinical features, radiation therapy procedures, and treatment strategies may have contributed to variances in survival outcomes. Hence, our phase 3 multicenter randomized controlled trial would help resolve this dispute. Among this group of 146 patients, who were monitored for a median period of 46 months, the use of moderately hypofractionated radiotherapy (Hypo-RT) with hormone therapy (HT) was found to be linked with better overall survival (OS) and progression-free survival (PFS) compared to conventional radiotherapy (Con-RT) using intensity-modulated radiation therapy (IMRT).

The importance of local disease control in patients with locally advanced non-small cell lung cancer (LA-NSCLC) following chemoradiotherapy cannot be emphasized enough, as it is directly linked to survival. [21] Additionally, local-regional failure (LRF) is responsible for around 35% to 40% of all first treatment failures. [28] A prior investigation has demonstrated that a higher intensity of radiation dosage is linked to enhanced local-

regional control (LRC). Specifically, for every 1 Gy increase in biologically effective dose (BED), the relative risk of local-regional failure (LRF) falls by around 3%. [11]

The current study suggests that the enhanced BED with Hypo-RT may have played a role in the observed increase in local-regional control (LRC), resulting in increased overall survival (OS). The PACIFIC study demonstrated that the use of durvalumab consolidation therapy resulted in a decrease in distant failures and an improvement in overall survival (OS). [6] The PACIFIC study has led to a shift in the therapeutic approach for inoperable stage III NSCLC, with a growing emphasis on combining radiotherapy (RT) with immune checkpoint inhibitors. [31-35]

Additionally, durvalumab was not yet accessible in China. Consequently, none of the patients in our research received consolidation immunotherapy. In a forthcoming trial, we will assess the effectiveness of Hypo-RT for inoperable stage III NSCLC in the context of immunotherapy.

In the context of IMRT, conformality in the physical dose distribution is achieved by using several subfields. During the administration of therapy, the subfield irradiation is carried out in a series of successive phases with varying intensities, which leads to an extension of the overall treatment duration. As a result, the amount of radiation absorbed by the tissue per unit of time and the pace at which the radiation is delivered reduces due to the machine's consistent output. This causes the tissue and cells to develop a higher resistance to radiation. On the other hand, hypofractionated therapy (HT) enables the irradiation of smaller areas to be done in a single procedure, potentially reducing the time needed to deliver the same amount of radiation to the tumour volume. In theory, rapidly finishing irradiation can minimize the impact of repairing sublethal damage, thereby enhancing the therapeutic benefit. [36,37] The findings of our investigation demonstrated similar levels of toxicity between Hypo-RT and Con-RT, which align with the majority of studies (with fraction doses ranging from 2.24-4 Gy) regarding the safety of Hypo-RT. Nevertheless, there were also significant occurrences of toxicity associated with Hypo-RT, such as radiation oesophagitis (14%-83.3%) and RP (3.3%-28.6%). [38-40]

By utilizing HT technology, the Hypo-RT group was able to enhance the safeguarding of patients' organs at risk (OARs), including the oesophagus, lungs, tracheobronchus, and heart, through the use of larger fraction sizes. When comparing IMRT to HT, it is found that HT offers dosimetric benefits such as improved dose conformity and sharper dose gradients. This enables the accurate administration of radiation doses to tumour locations with intricate structures, while minimising radiation exposure to healthy organs. [41-44]

Hypo-RT offers distinct practical benefits compared to traditional fractionation methods. Initially, the entire treatment plan might be accomplished within a shorter duration, offering enhanced convenience to the patient and a cost advantage to the public health system. Furthermore, it alleviates the burden on respiratory therapy units and conserves valuable time and medical resources for physicians.

Limitation of study

There are several constraints in the study that need to be acknowledged and resolved. Initially, our study was conducted with a limited number of participants, which might potentially affect the statistical power of the test. Although our findings appear encouraging, a more extensive study with a greater number of patients would be necessary to validate the advantages of Hypo-RT.

Additionally, PET/CT scans were not obligatory for the patients who were included in the study, both during their treatment and followup. Consequently, it is possible that some metastases, such as those in the mediastinum, may not have been detected. Furthermore, the absence of a blinded and unbiased evaluation of the raw data might potentially add some biases into the outcomes.

Conclusion

Our work demonstrates that Hypo-RT leads to better survival rates compared to Con-RT, without any additional harmful effects. This suggests that using mildly HypoRT (3 Gy/fraction) with accurate administration through HT with CCT is a secure and efficient therapeutic method in comparison to the existing standard treatment protocol. Additional research is needed to examine the effectiveness of HypoRT in combination with immunotherapy or targeted treatment.

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