

**IMPACT OF ESOPHAGEAL SPARING IMRT ON PATIENT  
REPORTED DYSPHAGIA OUTCOMES IN PATIENTS OF NON-  
SMALL CELL LUNG CANCER TREATED WITH RADICAL  
RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY**

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## **SYNOPSIS**

**Introduction** - Non-small cell lung cancer (NSCLC) accounts for approximately 80–85% of all lung cancers.<sup>1</sup> A major proportion (~60-70 %) of patients present with a locally advanced disease (locally or metastatic)<sup>2</sup>, where the standard of care is concurrent chemoradiotherapy (CCRT). Patients unfit for concurrent chemoradiotherapy are offered sequential chemoradiotherapy or radical radiotherapy alone.<sup>3</sup> While CCRT improves overall survival, it is associated with increased treatment-related toxicities, among which radiation-induced oesophageal toxicity is one of the most common and clinically significant dose-limiting adverse effects. With the adoption of IMRT, there is potential to reduce high-dose exposure to the oesophagus. Despite many advances, most studies have focused on physician reported toxicity. Data evaluating patient-reported dysphagia outcomes with oesophageal sparing IMRT using remains insufficiently studied.

**Aim and objectives** - To find out the incidence, severity and duration of development of acute dysphagia in patients of non-small cell lung cancer who have received radical radiotherapy alone with or without concurrent / sequential chemotherapy, with the use of oesophageal sparing IMRT.

**Material and methods** - A prospective observational study will be conducted at Tata Medical Centre, Kolkata, patients with locally advanced NSCLC planned for curative intent radical radiotherapy with or without concurrent or sequential chemotherapy using oesophageal sparing IMRT from June 2026 to Dec 2027 will be included. During the weekly on-treatment review clinic visits patients will complete the PRO-CTCAE questionnaire for difficulty and pain during swallowing while physicians will grade any dysphagia using CTCAE v.5. Data will be collected & managed using institutional REDCap electronic data capture tool after obtaining informed consent from the patient. Statistical analysis will be done using standard software R4.0. Percentage of agreement will be reported along with weighted Cohen's kappa as a measure of interrater agreement between patient reported difficulty in swallowing and maximum physician-graded dysphagia.

## **INTRODUCTION**

Lung cancer is among the most common cancers worldwide and a leading cause of cancer mortality.<sup>4</sup> In India , approximately 70,000–72,000 new lung cancer cases occur annually and around 66,000 deaths per year are attributed to lung cancer.<sup>5</sup> In India ,lung cancer accounts for ~5.9% of all cancers and ~8.1% of cancer-related deaths<sup>6</sup>

Concurrent chemoradiotherapy (CCRT) with or without sequential Durvalumab<sup>7</sup> or Ositmertinib<sup>8</sup> is the standard of care in stage III NSCLC (non-small cell lung cancer). Patients who are not candidates for CCRT are considered for sequential chemoradiotherapy (SCRT) or radical radiotherapy (RT) alone.

Since the oesophagus lies in the mediastinum, its proximity to the tumour and the involved lymph nodes in advanced stage makes it vulnerable to more damage during Thoracic RT. Acute esophagitis occurs during RT or within 3 months of its completion. Symptoms include dysphagia, odynophagia, retrosternal burning and weight loss. The currently used grading system for acute esophagitis is the grade 1-5 Common Terminology Criteria for Adverse Events (CTCAE) Version (5.0)<sup>9</sup>

Recent studies showed that concurrent chemotherapy and altered radiotherapy has improved overall survival and local control, however, higher incidence of severe esophagitis had been observed in patients using these treatment schemes<sup>10</sup>. With RT alone, the incidence of Grade  $\geq 2$  acute esophagitis has been found to lie between 5–20% and with Concurrent chemoradiotherapy it reaches 15–40%<sup>11</sup>. Grade 3 esophagitis accounts to 5–20% in CCRT trials<sup>12</sup>

With the advent of intensity-modulated radiotherapy (IMRT), efforts have focused on reducing high-dose oesophageal volumes while maintaining adequate target coverage.

In a study by Johnny Kao et al.<sup>13</sup> 43 patients out of a total of 82 patients with thoracic malignancies who had stage II–III non-small cell lung cancer were treated with definitive chemoradiotherapy. Intensity-modulated radiotherapy (IMRT) was delivered to 38 patients using a normal tissue-sparing approach. The study demonstrated significant reduction in oesophageal dose parameters with IMRT, with a decrease in acute grade  $\geq 2$  esophagitis from 81% to 35% in the advanced stage group while the overall cohort showed complete elimination of grade  $\geq 3$  esophagitis (0% vs 11%,  $p < 0.001$ ). Additionally, IMRT improved overall survival without increasing toxicity, highlighting its advantage over conventional techniques in reducing treatment-related oesophageal morbidity.

Large trials like RTOG0617<sup>14</sup> have demonstrated dose–toxicity relationship, with higher RT doses associated with increased oesophageal adverse events.

Oesophageal sparing aims to reduce the mean oesophageal dose, maximum dose (D max), V20 (the percentage of volume of organ receiving 20 Gy or more radiation), similarly V30,40etc.

Studies have reported that oesophageal-sparing approaches (a form of IMRT planning) reduce rates of clinically significant esophagitis when compared with IMRT alone<sup>16-19</sup>.

Acute Esophagitis is reported in 2 ways. By the patient himself or clinically noted by the physician. Treating physicians have been found to under-report the oesophageal symptoms or they tend to reserve reporting the adverse events for more severe symptoms. This usually undermines the treatment burden caused to patients and leads to inadequate and delayed management of treatment related toxicities.<sup>15</sup> Earlier symptom detection during RT may lead to timely supportive care interventions that may reduce treatment-related toxicity events.

The oesophageal toxicity under most of the investigations done so far, has usually been physician reported. In our study we aim to investigate the rates, duration and severity of ‘patient reported acute dysphagia’ in patients of non-small cell lung cancer using Oesophageal sparing IMRT who have been treated with Radical Radiotherapy with or without chemotherapy.

## **AIM AND OBJECTIVES**

### **Primary objective:**

To find out the incidence, severity and duration of acute dysphagia (anytime during radiotherapy to within 3 months after radiotherapy) reported by patients of non-small cell lung cancer using oesophageal sparing IMRT who have been treated with radical radiotherapy with or without chemotherapy.

### **Secondary objectives:**

1. To find out the concordance in grades and time to develop patient reported vs clinician reported acute dysphagia in patients of non-small cell lung cancer who have been treated with radical radiotherapy alone with or without concurrent or sequential chemotherapy

2. To evaluate the impact of oesophageal-sparing IMRT on cardiac substructure dosimetry in patients of non-small cell lung cancer who have received radical radiotherapy with or without concurrent or sequential chemoradiotherapy.

## **REVIEW OF LITERATURE**

In a prospective study by Li Ma et al,<sup>16</sup> eighty-seven patients with stage IIIA/B NSCLC who received definitive SIB-IMRT with a median dose of 65Gy (2.2-2.3 Gy per fraction ) and concurrent chemotherapy were analysed in two groups, one with oesophagus sparing technique, second without oesophagus sparing technique. The incidence of severe (Grade 3) was significantly lower in patients with oesophagus sparing technique ( $p = 0.002$ ). The use of oesophagus-sparing IMRT significantly reduced the incidence of Grade 3 esophagitis from 30.2% in the non-sparing group to 4.5% in the sparing group, with an absolute reduction of 25.7% ( $p = 0.002$ ) and a corresponding shift toward lower-grade (Grade 1–2) toxicity. Grade 2 esophagitis in the Sparing group was found to be 45.5% while in non-sparing group it was 53.5%.

Patients in the oesophagus sparing group had better nutrition status ( $p = 0.045$ ). With a median follow-up of 18 months, the 1-year, 2-year and 3-year OS of all the patients was 86.6, 65.4 and 43.7%. The 1-year, 2-year LRFS was 78.4, 65.9%. Hence it was concluded that Oesophagus-sparing technique is an effective and essential method to limit radiation esophagitis in LA NSCLC while maintaining the appropriate tumour coverage and clinical outcomes.

In a retrospective clinical and dosimetry study by Hani Al Halabi et al<sup>17</sup> the effectiveness of a contralateral oesophagus-sparing technique (CEST) in reducing radiation-induced esophagitis in patients with thoracic malignancies undergoing concurrent chemoradiotherapy (CCRT) was done. The study included 20 consecutive patients with locally advanced thoracic malignancies (predominantly NSCLC, ~80%). All patients received definitive IMRT with concurrent chemotherapy, with a minimum radiation dose of 63 Gy and a median dose of 70.2 Gy (range 63–72.15 Gy) delivered in 34–40 fractions.

The contralateral oesophagus (CE) was contoured as an avoidance structure, and a planning strategy was used to achieve spatial separation from the target volume. The median oesophageal mean dose was 23.1 Gy, and V60 was 5.3%, while the CE received significantly lower high-dose exposure (median V60 = 0.5%). The median CE V45 and V55 were 2.1 cc and 0.4 cc, respectively, demonstrating successful cross-sectional sparing. Clinically, the incidence of acute esophagitis was markedly reduced. Grade 1 and 2 esophagitis occurred in 55% and 20% of patients, respectively while no patient developed grade  $\geq 3$  esophagitis (0%, 95% CI: 0–16%), despite high radiation doses. The study suggested that sparing part of the oesophageal circumference may reduce severe toxicity without compromising target coverage. However, limitations included small sample size, lack of long-term outcomes (TCP/survival), and dependence on tumour geometry for feasibility of sparing.

Finally, it was concluded that CEST is a feasible and effective IMRT-based technique that significantly reduces severe esophagitis without compromising target coverage and recommended further validation through prospective trials.

In a retrospective dosimetric analysis by Małgorzata Łazar-Poniatowska<sup>18</sup> et al, the treatment plans of 13 patients with locally advanced, nonmetastatic NSCLC treated with definitive sequential or concurrent chemoradiation (60–66 Gy in 30–33 fractions) were studied. The contralateral oesophagus was delineated as a separate avoidance structure, and planning optimization was used to achieve a steep fall off across the section of oesophagus.

The use of Contralateral oesophageal -sparing technique resulted in a consistent reduction in oesophageal dose across all patients, with a mean oesophageal dose decreased by 3.8 Gy (range: 0.7–8.7 Gy). Significant reductions were observed in volumetric parameters, with V40 was reduced by 6.4% and V60 by 1.9%. However, there was no significant reduction in maximum oesophageal dose. Individual patient analysis confirmed consistent reductions in Dmean (e.g., up to –8.65 Gy). NTCP for oesophageal toxicity was reduced in all patients, with reductions ranging from 5% to 73%, indicating a clinically meaningful decrease in predicted complications. Despite these improvements, TCP remained largely unaffected, with variations ranging from –1.8% to +6.7%, confirming preservation of tumour control. The study concluded that CEST is an effective planning strategy to reduce oesophageal dose and NTCP without

compromising tumour control or target coverage in patients with locally advanced NSCLC undergoing definitive chemoradiotherapy.

In a phase 1 nonrandomized clinical trial by Sophia C Kamran et al<sup>19</sup>, 27 patients with thoracic malignancies (19 of them had non-small cell lung carcinoma, and 6 had small cell lung carcinoma ) received Intensity-modulated radiation therapy to 70 Gy at 2 Gy/fraction concurrent with standard chemotherapy with or without adjuvant durvalumab. The study evaluated the feasibility of oesophageal-sparing dose constraints during high dose chemoradiation. No grade >/3 esophagitis was observed in this small cohort, while 28% of the patients developed grade 2 esophagitis. The median follow-up was 33.3 months.

The 2-year progression-free survival and overall survival rates were 57% and 67%. This study found that the CE-sparing technique was associated with reduced risk of esophagitis, although the findings get limited by the small sample size and mixed patient population.

## **MATERIAL AND METHODS**

**Study design** - Prospective Observational Study

**Study setting** - Department of Radiotherapy of a tertiary cancer centre in Eastern India.

**Target population** - The target population of the study is patients with locally advanced NSCLC who are planned for curative intent radical radiotherapy using Intensity Modulated Radiotherapy with or without concurrent or sequential chemotherapy.

### **Sample size calculation:**

Between June 2026 to Dec 2027, 40 patients of locally advanced non-small cell lung cancer will be recruited prospectively for this study. As per the existing data, 15–20% of the patients experience grade 3 or greater esophagitis during radiotherapy for lung cancer. We need a sample size of 40 patients to determine that 20% of the patients treated in the cohort will develop grade III esophagitis with a 95% confidence interval and 10% absolute error. This number is also based upon the number of non- small cell lung cancer patients registered for radical radiotherapy in the last few years at our centre.

**Inclusion Criteria:**

1. Patients of locally advanced non-small cell lung cancer who will be treated with radical radiotherapy alone or concurrent chemoradiation or sequential chemoradiation.
2. All patients who will be receiving Oesophageal sparing Intensity modulated radiotherapy (IMRT) with daily image guidance.

**Exclusion criteria:**

Patients who will receive:

1. Post operative radiotherapy
2. Palliative radiotherapy
3. Stereotactic body radiotherapy (SBRT) for early NSCLC
4. Reirradiation
5. Radiotherapy for small cell lung cancer
6. Patients who will receive 3D conformal radiotherapy (3DCRT) for NSCLC
7. Consolidative radiotherapy for oligometastatic disease

**Registration and consenting:**

Subjects must meet all the inclusion criteria and none of the exclusion criteria to be eligible for this trial/study. Subjects must be registered and consented before starting the study treatment.

**Withdrawal Criteria:**

A patient may or be withdrawn from study treatment for the following reasons:

1. Any disease which prevents further follow up.
2. The patient decides to withdraw the consent voluntarily.
3. Any personal concern in the patient's situation which requires the patient to discontinue the follow up.

If a patient or investigator decides to stop the study treatment then the patient's health status will be periodically reviewed via continued study visits or phone contact, or from their general practitioner or medical records to allow collection of data outcomes. If a patient withdraws from the study entirely, the effective date of the notification will be the date on which their



withdrawal is received by the study team. No information about the patient will be collected from that point in time onwards but any information collected prior to that date can be used and forms part of this study.

### **Work up:**

All patients with suspected lung cancer will be staged using computed imaging, and histological or cytological diagnosis will be obtained. Patients with no obvious metastases will be further staged using a whole-body fludeoxyglucose-positron emission tomography (FDG-PET) scan and magnetic resonance imaging (MRI) of the brain. Pulmonary function tests comprising forced expiratory volume in 1 s and lung diffusion capacity for carbon monoxide (DLCO) or the six minute walk test will also be carried out to assess fitness for radical radiotherapy. All patients will be discussed at the lung cancer multidisciplinary team (MDT) meeting, and the optimum course of treatment will be discussed and decided upon. Patients who will be unresectable because of staging or technical reasons or medical reasons (comorbidities) or who will decline surgery will be considered for radical radiotherapy.

Concurrent chemo-radiotherapy+/-Durvalumab/Osimertinib depending upon molecular status (EGFR/Alk/PDL-1) will be delivered to the patients who will be considered fit enough to tolerate this treatment. For patients who will be comparatively frail or less fit, sequential chemo-radiotherapy will be offered. For patients who will not be suitable for chemotherapy because of comorbidities or will have contraindications to chemotherapy, radiotherapy alone will be used.

### **Radiotherapy protocol:**

Concurrent chemoradiotherapy (CCRT) will be delivered using conventional fractionation at 2 Gy per fraction (usually 60 Gy in 30 fractions over 6 weeks), whereas sequential chemoradiotherapy (SCRT) will be delivered using either accelerated hypofractionated radiation (55 Gy in 20 fractions over 4 weeks, at 2.75 Gy per fraction) or conventional fractionation. Most RT-alone treatments will be accelerated hypofractionated radiation (55 Gy in 20 fractions over 4 weeks, at 2.75 Gy per fraction).

The length of the oesophagus is defined to extend from the inferior border of the cricoid cartilage to the gastro-oesophageal junction. All patients will undergo simulation using four-dimensional computer tomography (4DCT) to account for respiratory motion. Patients will be immobilised in the supine position using appropriate immobilisation devices. The gross tumour

volume will include the primary tumour involved and lymph nodes identified on the imaging. The details of oesophagus sparing technique would include: 1. A uniform 5mm margin will be added to the ITV to create the clinical target volume (CTV) to account for the microscopic spread. A further 5 mm margin will be added to the CTV to generate the planning target volume. (PTV) to account for setup uncertainties. dose).

Treatment planning will be performed using intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques with emphasis on oesophageal sparing without compromising target coverage. For patients receiving 60 Gy in 30 fractions, oesophageal dose constraints will include a maximum dose (Dmax) less than 105% of the prescribed dose, mean dose (Dmean)  $\leq 34$  Gy (optimal  $\leq 25$  Gy), V40  $\leq 40\%$  (optimal  $\leq 25\%$ ), V50  $\leq 30\%$  (optimal  $\leq 20\%$ ), V55  $\leq 25\%$  (optimal  $\leq 18\%$ ), and V15  $\leq 55\%$  (optimal  $\leq 45\%$ )(Appendix1) For patients receiving 55 Gy in 20 fractions, biologically equivalent dose adjustments will be made using the linear quadratic model with an  $\alpha/\beta$  ratio of 3 Gy (EQD2  $\approx 63$  Gy), and corresponding constraints will include Dmax  $< 55$  Gy, Dmean  $\leq 32$  Gy (optimal  $\leq 24$  Gy), while maintaining equivalent volume-based constraints (Refer Appendix).

### **Concurrent chemotherapy protocol:**

The concurrent chemotherapy will be typically delivered with standard fractionation (2 Gy/fraction) and usually comprises cisplatin and etoposide or carboplatin and paclitaxel weekly. Most patients will receive cisplatin 50 mg/m<sup>2</sup> intravenously on days 1, 8, 29, and 36 with etoposide 50 mg/m<sup>2</sup> intravenously on days 2–5 and 29–33. The etoposide on days 2–5 and 30–33 will be changed to 100 mg/m<sup>2</sup> orally, for patient convenience and easing chemotherapy workload. When planning with Carboplatin and Paclitaxel, Carboplatin AUC 2 and Paclitaxel 50 mg/m<sup>2</sup> weekly will be delivered along with radiation.

### **Sequential chemotherapy protocol:**

3-4 cycles of platinum doublet-based chemotherapy followed by external beam radiotherapy (55Gy/20fractions/4weeks) will be planned.

### **Review visits:**

During radiotherapy, sequential chemoradiotherapy or concurrent chemoradiation, the patients will be seen and reviewed by a clinical oncologist on a weekly basis and will be assessed for any toxicity and treated as appropriate. During weekly visits in radiotherapy review clinics

patients will complete PRO CTCAE version 1 items with a recall period in the last 7 days. Similar patient reported outcomes will also be assessed at 6 weeks and 3 months after completion of radiotherapy during their follow ups. Patients will report their perceived severity of swallowing difficulty/heartburn/pain during swallowing on a 5-point descriptive scale: none, mild, moderate, severe, and very severe. Patients will complete PRO-CTCAE questions using electronic tablets or paper printed question templates. The responses will be reported under guidance of an oncology nurse present in the review clinic. Additionally patient reported outcomes of few other acute problems during radiotherapy treatment will also be recorded using PRO-CTCAE questions.

During weekly on-treatment review clinic visits, physicians grade dysphagia/difficulty swallowing using the 5-point CTCAE v.5 scale will also be recorded. Similar clinician reported outcomes will also be assessed at 6 weeks and 3 months after completion of radiotherapy during their follow ups. Before providing a toxicity grade, physicians will review routine objective measures for on-treatment toxicity assessments, including vital signs, weight, physical examination, and RT dose received. PRO-CTCAE item scores for each toxicity will be transformed into CTCAE grades based on the guidelines provided by Basch et al<sup>20</sup> Note that concordance between the patient reported outcomes and physician reported outcomes is not guaranteed. All study data will be collected and managed using REDCap electronic data capture tools hosted at Tata Medical Centre.<sup>2122</sup> Electronic patient reported outcomes will be collected using the e-PROM solution developed by the department.

### **Follow up:**

After completion of treatment, the patients will be seen after 6 weeks to ascertain whether the side effects are settling as expected. Post treatment response assessment CT is carried out at 3 months after treatment completion and response will be documented according to the RECIST 1.1 criteria.<sup>23</sup>

### **Statistical analysis:**

Statistical analysis will be conducted using a standard statistical software R 4.0. Week-wise availability of clinician and patient reported radiation esophagitis outcome data will be reported along with number and proportion of missing data. Proportions will be reported along with binomial 95% confidence intervals.

Week-wise and during follow-up (1st and 2nd) proportions of patients who experience CTCAE (version 5) defined acute esophagitis will be reported for each grade. Graphical plots depicting the trajectory of the change in the grade of toxicity will also be shown. Similar descriptive and graphical analysis will be undertaken for patient reported outcomes (according to PRO-CTCAE). The maximum severity of patient reported radiation induced esophagitis during radiotherapy treatment and also the time to first report of patient reported moderate radiation esophagitis symptoms outcome will be recorded. We will also estimate the week-wise and overall concordance between the patient reported and clinician esophagitis grades. Percentage of agreement will be reported along with weighted Cohen's kappa as a measure of interrater agreement. Cohen's kappa will evaluate the agreement between maximum patient reported difficulty in swallowing and to maximum physician-graded dysphagia at any time during treatment. Cohen's kappa will be reported along with the 95% confidence intervals of the same. Cohen's kappa is being reported as for the purpose of this analysis patient reported moderate to severe toxicity would be considered concordant to clinician reported Grade 2 to 3 toxicity. Physician reported Grade 0 - 1 toxicity would be considered concordant to patient reported none or mild toxicity. Additional analysis of concordance between physician reported and patient reported toxicities will also be undertaken where a more ordinal structure of reporting will be retained viz. Physician reported Grade 0, grade 1, grade 2 and grade 3 toxicity would be considered concordant to patient reported no toxicity, mild toxicity, moderate toxicity and severe toxicity respectively.

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## APPENDIX

### Oesophageal dose constraints:

	60 Gy in 30fr (optimum)	60 Gy in 30 fr (mandatory)	55 Gy in 20 fr (optimum)	55 Gy in 20 fr (mandatory)
Dmax	<60 Gy	<60 Gy	<55Gy	<55Gy
D mean	<25Gy	<34Gy	<24Gy	<32Gy
V40	<25%	<40%	<24%	<38%
V50	<20%	<30%	<19%	<29%
V55	<18%	<25%	<17%	<24%
V15	<45%	<55%	<43%	<53%