MOHAMMAD GOURAN SAVADKOOHI

MASTER OF SCIENCE THESIS

Tumor and treatment parameters influencing radiotherapy outcomes in locally advanced (LA) non-small cell lung cancer (NSCLC).

Analysis of institutional and population data from the province of Ontario, Canada.

By Mohammad Gouran-Savadkoohi, MD

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Health Sciences

Descriptive Note

McMaster University, Master of Medical Sciences (2022) Hamilton, Ontario, Canada.

Title: Tumor and treatment parameters influencing radiotherapy outcomes in locally advanced (LA) non-small cell lung cancer (NSCLC). Analysis of institutional and population data from the province of Ontario, Canada.

Author: Mohammad Gouran-Savadkoohi, M.D.

Supervisor: Dr. Theodoros Tsakiridis

Number of pages: XVI, 108

Lay Abstract

Lung cancer is the leading cause of cancer death in Canada and worldwide. These tumors are present as two main histological types, small cell and non-small cell lung cancer, the latter of which consists the majority of the cases diagnosed. Although treatments with surgery or radiotherapy provide reasonable outcomes in lung cancer cases detected early, a high proportion of patients present with localized but advanced disease that is inoperable. Over the last three decades, treatment of locally advanced non-small cell lung cancer has evolved from radiation alone to chemoradiation and immunotherapy. These developments have increased the survival of these patients. In this thesis, we tried to dissect the elements that play roles in the survival of locally advanced non-small cell lung cancer patients. To do this, we evaluated such patients at two levels. First, at the provincial level, we evaluated the type of treatments, and we explored the association of metabolic imaging with positron emission tomography (PET) and the use of high-dose chest radiotherapy with patient survival. Second, at the institutional level, we assessed patients' outcomes with a more detailed approach. We analyzed the type of treatment along with a detailed dosimetric analysis. The results of our analysis suggest that the use of PET scans and curative radiotherapy is associated with improved survival. On the other hand, the unintentional treatment of the heart with increasing doses of radiotherapy, taking place during chest radiation for lung cancer, is associated with poor outcomes. These results provide a basis for further investigation to improve outcomes of radiotherapy in this disease.

Abstract

Introduction

Lung cancer is the leading cause of cancer death worldwide. In Canada, in 2021 alone, an estimated 21,000 patients have died from this disease. Non-small cell lung cancer (NSCLC) constitutes 85% of all lung cancer cases diagnosed. Over the past 30 years, treatment of unresected locally advanced (LA)-NSCLC evolved from treatment with chest radiotherapy (RT) alone to the current standard of care (SOC) of concurrent chemo-radiation (cCRT), followed by consolidative immunotherapy. Modern RT has influenced the survival of LA-NSCLC patients. In this work we analyzed data from provincial and local institutional databases to evaluate whether, i) the use of modern imaging with ^{18}F-deoxyglucose (FDG)-positron emission tomography (PET), ii) dose of chest RT to tumors and iii) unintentional irradiation of normal tissues during treatment for lung cancer, influence outcomes of patients managed with RT.

Methodology

Ontario provincial databases were searched through the Institute of Clinical Evaluative Sciences (IC/ES) for stage III NSCLC patients diagnosed between 2007 and 2017. Surgical patients were excluded, and all patients that received RT with or without chemotherapy were selected. Patients were divided into groups of different RT doses (<40Gy, 40-55.9Gy, and ≥56Gy) and whether they underwent diagnostic FDG-PET. For the next study phase (the institutional level), we retrospectively identified and reviewed LA-NSCLC patients treated at local health integration network area 4 (LHIN4) cancer centres (Juravinski and Walker Family Cancer Centres) from 2009 to 2019. We selected patients treated in that period with chest RT $\geq$ 40Gy with or without chemotherapy. Patients' data were reviewed individually for disease characteristics, staging

investigations, RT treatment parameters and survival outcomes. Dosimetric analysis was performed on both groups of patients (RT alone group and cCRT group).

Results

The provincial analysis included 5,577 stage III patients who had received chest RT without surgery between January 2007 and March 2017. Within this group, 39.8% (2,225) received RT alone, 47.4% (2,645) received concurrent chemo-radiotherapy (cCRT), and 12.6% (707) received sequential chemo-radiotherapy (sCRT). Median overall survival (OS) with RT alone in three dose groups <40Gy, 40-55.9Gy, ≥ 56Gy was 7.2, 8.5 and 13.3 months compared to 16.5, 15.8 and 22 months for cCRT patients. Higher RT dose and PET utilization were independently associated with improved survival in multivariate analysis.

At the institutional analysis, 84 patients were treated with RT alone, 184 with cCRT and patients with sequential CRT were excluded. In the RT alone group, the median, 1- and 3-year overall survival were 18.1 months, 64.4% and 24.3%, respectively. In comparison, the median, 1- and 3-year survival outcomes in the cCRT group were 36.3 months, 82.5%, and 50.4%, respectively. Additionally, 79.8% of patients in the radiation alone group and 95.1% in cCRT group had PET staging. In univariate analysis, the RT dose prescribed to the tumor and RT dose delivered to the heart were significantly associated with survival, while multivariate analysis only showed the significant association between RT dose to heart and overall survival.

Conclusions

Our population-based analysis confirmed that radiation monotherapy remains a widely used treatment modality in LA-NSCLC. Higher RT doses and utilization of FDG-PET imaging are associated with improved survival in patients with unresected LA-NSCLC managed with RT. The

institutional analysis suggests that in well-staged patients with LA-NSCLC, chest RT of ≥40Gy is associated with improved survival outcomes that compare favorably with historical results of definitive RT alone treatment. Further, survival of patients staged well with FDG-PET and treated with SOC cCRT was higher than historical reports. Importantly, in this study we found that RT dose delivered to the heart associates negatively with patient survival. These findings can help improve clinical decision-making in the management of unresected LA-NSCLC and can serve as basis for future clinical trials.

Acknowledgment

First, I would like to express my sincere gratitude to my supervisor and mentor, Dr. Theos Tsakiridis, for the thoughtful comments, recommendations, and guidance during this research. Your continued advice, support and encouragement have been invaluable throughout this study. Also, I would like to express my gratitude and appreciation to Dr. James Wright for being a part of my supervisory committee. I'm grateful for your insight and suggestions to improve the project's overall outcome. Also, I would like to thank Dr. Gregory Pond for sacrificing his time on top of what would be a full schedule.

I should also note that provincial analysis study has been accepted for publication in Journal of Thoracic Disease.

Thank you to the physics team in Juravinski Cancer Centre; without you, the completion of this project would certainly not be feasible. Specifically, Dr. Orest Ostapiak for the dosimetric analysis of institutional study.

Finally, I would like to thank my father and mother, Dariush and Belgheys, my wife Elham, my sister Samira, and all my family members for their unconditional support during these years.

TABLE OF CONTENTS

List of Figures and Tables

List of Tables

List of Figures

List of Abbreviations

ALK: Anaplastic Lymphoma Kinase

BRAF: v-raf Murine Sarcoma Viral Oncogene Homolog B1

CBCT: Cone Beam CT

CCO: Cancer Care Ontario

cCRT: Concurrent Chemoradiation

CFRT: Conventional Fractionation Radiotherapy

COPD: Chronic Obstructive Pulmonary Disease

CRT: Chemoradiation

CT: Computed Tomography

EBUS: Endobronchial Ultrasound

EBUS-TBNA: Endobronchial Ultrasound Transbronchial Needle Aspiration

EGFR: Epidermal Growth Factor Receptor

EUS: Endoscopic Ultrasound

FDG: Fluorodeoxyglucose

FDG-PET: Fluorodeoxyglucose -Positron Emission Tomography

FISH: Fluorescence In Situ Hybridization

H&E: Hematoxylin and Eosin

HFRT: Hypofractionation Radiotherapy

ICI: Immune Checkpoint Inhibitors

IGRT: Image-Guided Radiation Therapy

IHC: Immunohistochemistry

IMRT/VMAT: Intensity-Modulated RT/Volumetric Modulated Arc Therapy

KRAS: Kirsten Rat sarcoma Viral oncogene homolog

LA-NSCLC: Locally Advanced Non-Small Cell Lung Cancer

mOs: Median Overall Survival

NGS: Next Generation Sequencing

NLST: National Lung Screening Trial

NSCLC: Non-Small Cell Lung Cancer

NSCLC NOS: Non-Small Cell Lung Cancer Not Otherwise Specified

OARs: Organs At Risks

OS: Overall Survival

PD-L1: Programmed Death Ligand 1

PET/CT: Positron Emission Tomography/Computed Tomography

PFS: Progression Free Survival

RT: Radiotherapy

SBRT: Stereotactic Body Radiotherapy

sCRT: Sequential Chemo-Radiotherapy

TTF-1: Thyroid Transcription Factor-1

TTNA: Trans Thoracic Needle Aspiration

3D: Three-Dimensional

4D CT: Four-Dimensional Computed Tomography

Declaration of Academic Achievement

Contributions to concepts and design of research: Dr. Mohammad Gouran Savadkoohi, Dr. Theos Tsakiridis, Dr. James Wright, and Dr. Gregory Pond

Contributions to data interpretation: Dr. Mohammad Gouran Savadkoohi, Dr. Theos Tsakiridis, Dr. James Wright, and Dr. Gregory Pond

To the best of my knowledge, the content of this document does not infringe on anyone's copyright.

Chapter I - Background

1. General introduction

Lung cancer is the leading cause of cancer death worldwide (1). In 2021 alone, an estimated 21,000 patients are expected to have died of lung cancer in Canada alone (Canadian Cancer Statistics). Lung cancer incidence and mortality rates increase dramatically with age. Incidence rates peak among Canadians aged 75 to 84 years (396 per 100,000 people), while mortality rates peak among Canadians aged 85 years and older (366 per 100,000 people). Overall, the lung cancer incidence rate is 1/10 higher among men than women, and the mortality rate is almost 1/3 higher among men than women. However, for Canadians younger than 55 years, rates are higher among women than men (2).

The most common symptoms associated with lung cancer include cough, hemoptysis, dyspnea, chest discomfort and chest pain(3).

1.1 Risk factors for lung cancer

One of the primary risk factors associated with lung cancer is smoking. Tobacco smoking is associated with cancer deaths (4, 5). Carcinogenic chemicals are often present in cigarette smoke (5). The risk of lung cancer is related to the number of cigarettes. Nonsmokers exposed to smoke (passive smokers) are at risk of developing lung cancer (6).

Other risk factors associated with lung cancer are lung disease (like COPD), cancer history, exposure to carcinogens and family history of lung cancer. Several agents are known to cause lung cancer. Cadmium, asbestos, silica, beryllium, and arsenic are associated with lung cancer risk (7, 8). Radon gas is also related to lung cancer risk (5, 8).

1.2 Lung cancer spread and metastasis

Centrally located lung cancer spreads by direct extension proximally and distally along the bronchus of origin and may extend to the trachea as well as growing into the pulmonary parenchyma and subsequently extending to the mediastinum or pleura. Pleural involvement leads to extension into the chest wall and diaphragm. Vascular invasion is very common (over 80% of the cases), which leads to extensive tumor emboli and cor pulmonale (9). It has been reported that tumor cells can spread through air spaces, resulting in secondary tumor deposits at some distance from the main mass (10) . Figure 1.1 depicts lung tumor extension pathways based on eighth edition of TNM staging (11) .

Lymph node metastases occur first in the interlobar and hilar region, then in the mediastinal and lower cervical (supraclavicular) groups, and less commonly in axillary and subdiaphragmatic sites (12). Figure 1.2 shows the node map for lung cancer developed by International Association for the study of lung cancer (IASLC) (13).

The common sites for distant metastases are liver, other areas of lung, adrenal, bone and bone marrow, kidney, and central nervous system (14).

Additionally, brain metastases are more common in adenocarcinoma histology and may be the first manifestation of the disease (15).

Figure 1.1 Pathways of lung tumor progression (Based on eighth edition of TNM staging) (adopted from Lababede et al (2018) (11)

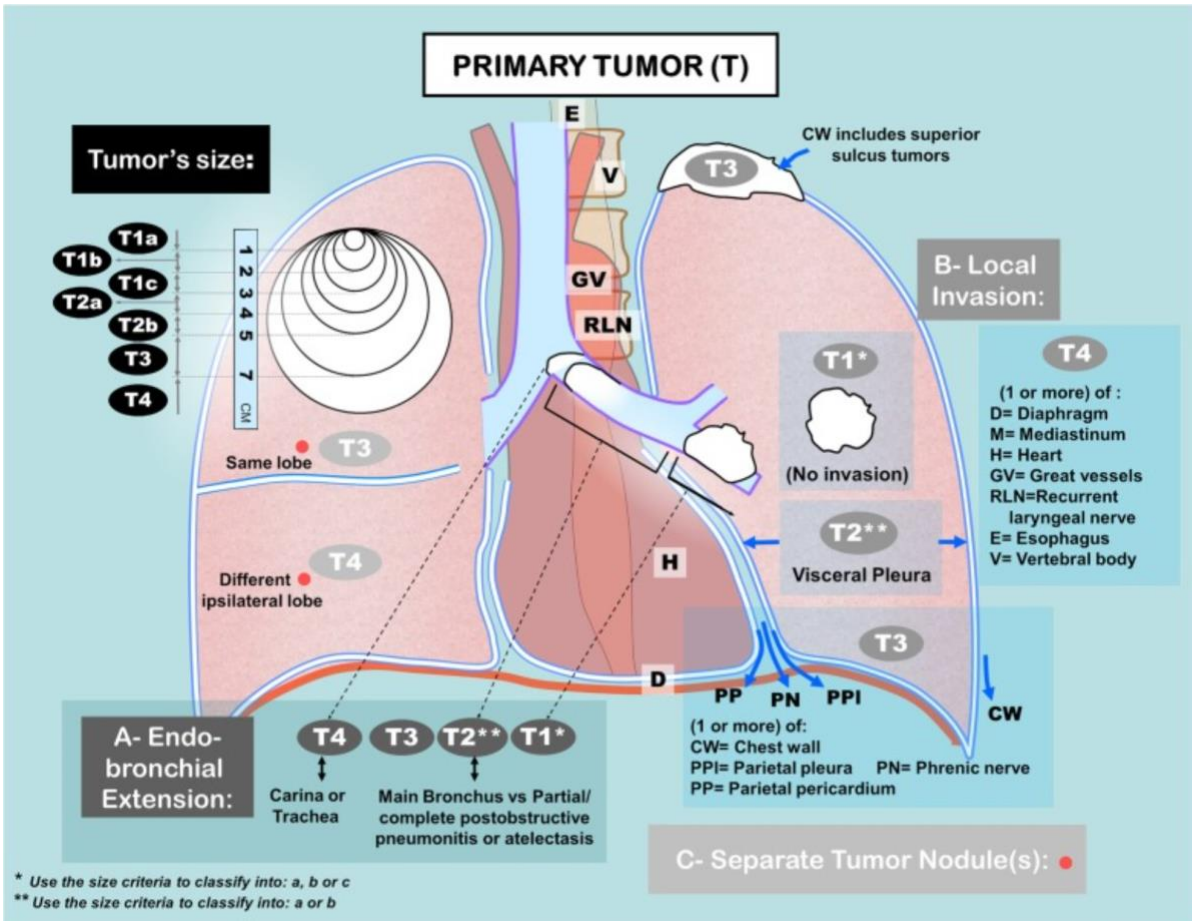
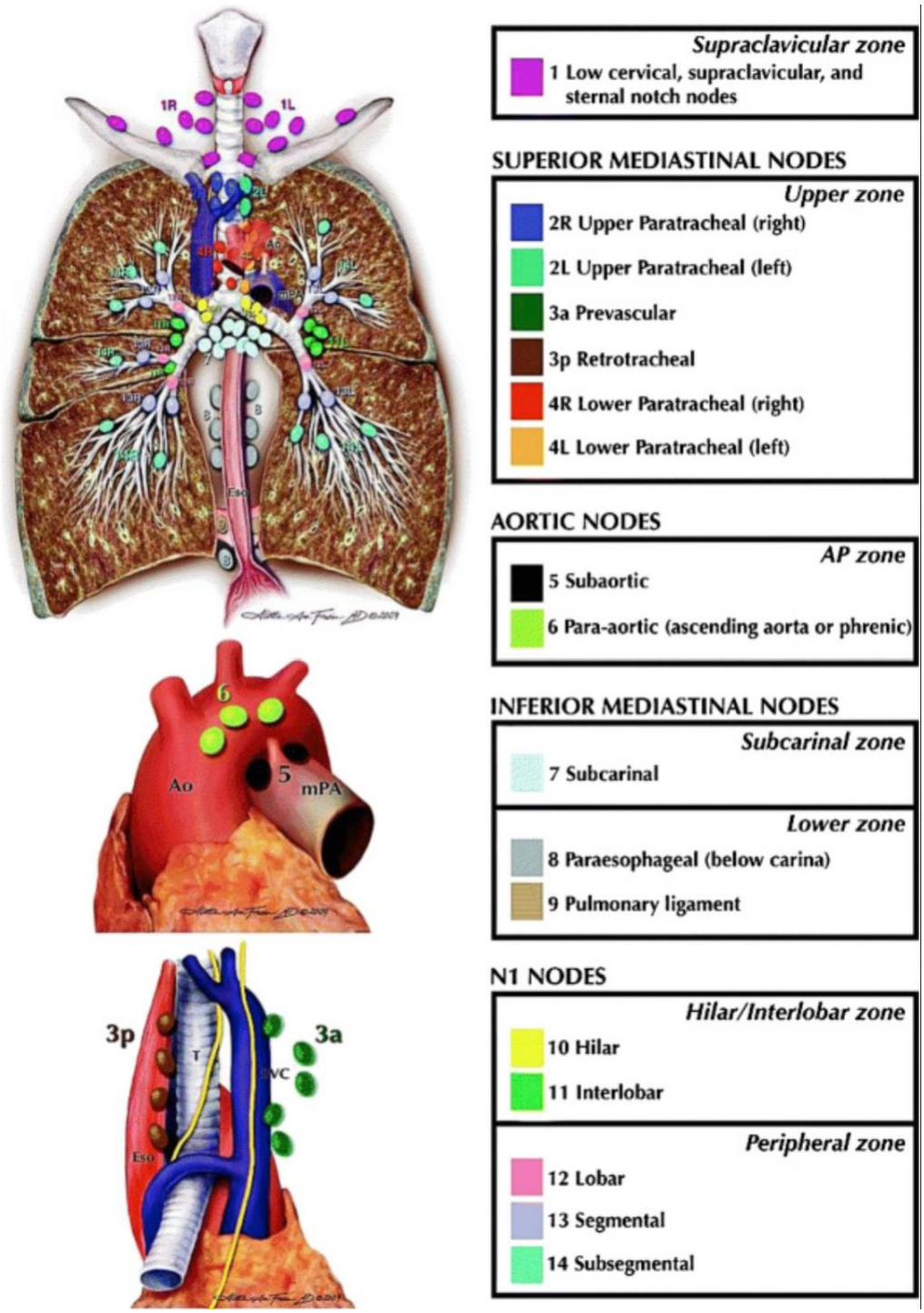


Figure 1.2 Lymph map for lung cancer developed by the International Association for the Study of Lung Cancer (IASLC) (Detterbeck et al (2017)(13)

.



1.3 Lung Cancer screening

Unfortunately, a significant proportion of lung cancer patients are diagnosed in the advanced stage (50% of cases are diagnosed with stage IV disease). Early diagnosis is critical since the early-stage disease has a higher cure rate. The national lung screening trial (NLST) was conducted to assess the benefit of low-dose CT scans in comparison with chest radiographs for detecting lung cancer (16). This trial showed that current or former smokers with a 30 or more pack-year smoking history aged between 55-74 benefited from a low dose chest CT scan. It was shown that this intervention would decrease lung cancer mortality by 20%. Different task forces in the United States have recommended CT-based screening. In Canada, Cancer Care Ontario recommends lung cancer screening for patients between 55-74 who have smoked for at least 20 years.

1.4 Diagnostic Evaluation

Different factors should be considered to choose the optimal diagnostic method, including method sensitivity and specificity. Invasiveness and the risk of the procedure itself should also be considered, especially when patients have high comorbidities.

The confirmed diagnosis is based on pathologic evaluation of tissue samples. Obtaining tissue specimens is a complex procedure that depends on various factors, from the patient's performance status and comorbidities to the location of the lesion and radiographic appearance. On the other hand, the adequacy of the tissue volume is essential, since many decisions depend on molecular tests which require satisfactory tissue amount. Frequently, minimally invasive techniques are used to obtain specimens in patients with unresectable advanced disease. However, diagnosis may be more difficult when using small tissue biopsies. In patients with suspected lung cancer, many techniques can help obtain tissue, including sputum cytology, bronchoscopy with biopsy and

transbronchial needle aspiration, thoracocentesis, mediastinoscopy, video-assisted thoracic surgery, open surgical biopsy and image-guided transthoracic needle core biopsy. Other diagnostic tools that provide tissue are EBUS-guided biopsy, EUS-guided biopsy, navigational bronchoscopy and robotic bronchoscopy.

Different clinical scenarios can be anticipated; patients with central mass with possible endobronchial involvement should undergo bronchoscopy, and those with peripheral nodules may benefit from navigational bronchoscopy, transthoracic needle aspiration or radial EBUS (17).

On-site evaluation should be used, when available, to ensure transbronchial needle aspirates or EBUS results are adequate for diagnosis and biomarker testing.

In nodal involvement, EBUS provides access to 2R/2L, 4R/4L, 10R/10L and perhaps other hilar nodal areas (See Figure 1.2). In the case of clinical (PET or CT) positive mediastinal involvement, a negative EBUS-TBNA does not rule out malignancy, and a mediastinoscopy is warranted before surgical resection. Lymph node stations in stations 5, 7, 8 and 9 can be biopsied by EUS guidance. Trans Thoracic Needle Aspiration (TTNA) and anterior mediastinotomy provide access to stations 5 and 6 lymph nodes if clinical suspicion is present. In general, mediastinal lymph nodes should be sampled systematically to determine the staging and therapeutic options.

In case of pleural effusion, thoracentesis is necessary; this may be followed by thoracoscopic evaluation of pleura if the cytology comes back negative and curative-intent treatment is considered.

Usually, concomitant staging is helpful since it avoids additional procedures. It is preferable to take the biopsy of the lesion that would confer the highest stage (Biopsy from a suspected metastasis than from a primary lesion). FDG-PET/CT scan should be performed before choosing

a diagnostic biopsy site, especially in case of clinical suspicion for advanced-stage disease. For a successful biopsy, expertise availability is another important factor for consideration.

As noted above, patients with the solitary metastatic site should have tissue confirmation of that site. In case of multiple site involvement, at least one site should be biopsied before proceeding to treatment. In case of difficulty in the biopsy of the metastatic site, primary lesion or mediastinal lymph node should be biopsied.

1.5 Pathologic Evaluation of Lung Cancer

Pathologic evaluation reveals tumor origin (primary lung cancer vs metastatic cancer), the histologic type and surrounding tissue involvements and aids biomarker studies to assess for actionable somatic, disease-associated variants/mutations (EGFR mutations) or immune biomarkers (PD-L1).

The patient may benefit from targeted therapy if specific driver mutations are identified (such as EGFR mutations).

As for all pathologic specimens, lung biopsies should be assessed morphologically, including routine staining approaches such as hematoxylin and eosin (H&E) staining.

The main concern in the histologic evaluation of lung cancer is distinguishing adenocarcinomas from squamous cell carcinomas.

Immunohistochemistry (IHC) can aid in differentiating adenocarcinoma, squamous cell carcinoma and metastatic versus primary malignancy. Primary pleural mesothelioma is another possible pathologic finding, especially when a pleural biopsy is taken. Other benign lung conditions may need to be ruled out, such as fungal infection or tuberculosis.

Intraoperative pathologic evaluation is frequently needed, especially when surgical resection margin status is unknown during lobectomy or pneumonectomy. Moreover, intraoperative evaluation is frequently required when regional lymph nodes need to be evaluated. Additionally, in the case of incidental nodules, intraoperative assessment can help significantly.

Detailed histopathologic evaluation is necessary for classifying tumor type, staging, and prognostic factors. The surgical pathology report should include the WHO histologic classification for lung carcinomas, which was developed through international panels. IHC and molecular studies were recommended.

Major subtypes of NSCLC include adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma, and less common subtypes. It is recommended that NSCLC should be classified as subtypes based on WHO guidelines.

Preferably, the subtype should be specified. General terms like non-small cell carcinoma, not otherwise specified, should be used infrequently and only when a more specific diagnosis cannot be obtained by morphology or confirmatory staining.

Molecular testing for patients with metastatic NSCLC has crucial value, which is strongly recommended for patients with metastatic adenocarcinoma, large cell carcinoma, and NSCLC (NOS), and should be considered for patients with metastatic squamous cell carcinoma, too.

One of the core tastings that should be part of every pathologic evaluation in the metastatic setting is PD-L1 IHC testing.

1.5.1 Adenocarcinoma

Adenocarcinomas constitute almost 40% of NSCLC. This pathologic subtype is the most common NSCLC subtype. Classes for adenocarcinoma include:

1. Adenocarcinoma in situ, which is a typically solitary lesion that is usually non-mucinous;
2. Minimally invasive adenocarcinoma (MIA), which is a solitary and discrete non-mucinous lesion with a maximum area of invasion no greater than 0.5 cm
3. Invasive adenocarcinoma (including various variants)

AIS and MIA are associated with better survival, especially if they are resected early(18). Diagnosis of AIS, MIA and large cell carcinoma should be based on the completely resected lesion and should be avoided on small sample biopsies.

1.5.2 Squamous cell carcinoma

Squamous cell carcinoma is a malignant epithelial tumor showing keratinization and intercellular bridges in well differentiated tumors. These features cannot be identified easily in poorly differentiated tumors, but they show markers of squamous cell differentiation in the IHC evaluation.(19)

1.5.3 Adenosquamous cell carcinoma

Tumors with mixed adenocarcinoma and squamous cell carcinoma components are called adenosquamous carcinomas; each component should constitute at least 10% of the tumor. In cases of squamous cell carcinoma with an adenocarcinoma component, molecular testing is recommended.

1.5.4 Large cell carcinoma

Large cell carcinomas are malignancies that lack morphologic or IHC characteristics of any clear lineage; these tumors do not express markers of squamous cell carcinoma, adenocarcinoma or

small cell carcinoma. Diagnosing large cell carcinoma requires a carefully resected tumor and should not be made on non-resected tissue samples or cytologic specimens.

1.5.5 Small cell carcinoma

Small cell carcinoma is a major subtype of pulmonary neuroendocrine tumors. Small cell carcinoma can be diagnosed using hematoxylin and eosin (H&E) staining, characterized by small blue cells with scant cytoplasm, high nuclear to cytoplasmic ratio, granular chromatin, and inconspicuous nucleoli. These cells are round, oval, or spindle-shaped, revealing high mitotic figures.

Another subtype of neuroendocrine tumors is carcinoid tumor. Care should be taken to properly distinguish typical carcinoids from atypical carcinoids by assessing for necrosis and using a morphologic mitotic count. These tumors should be treated based on neuroendocrine tumor guidelines.

1.5.6 Immunohistochemistry for Diagnosis of NSCLC

Although IHC evaluation can be used to differentiate adenocarcinoma, squamous cell carcinoma, metastatic malignancy, and other possible tumors in the differential diagnosis, but Judicious use of IHC is strongly recommended for NSCLC diagnosis in biopsy specimens to save tissue for molecular analysis.

Diagnosis of poorly differentiated NSCLC in small biopsy can be challenging, but often IHC can help. Specific pathologic subtypes have distinctive IHC patterns(18, 20).

80%-90% of primary pulmonary non-mucinous adenocarcinomas are positive for thyroid transcription factor-1 (TTF-1); while squamous cell carcinomas are often negative for TTF-1 and positive for p40 or p63(20). Metastatic adenocarcinoma is usually negative for TTF1, except for thyroid malignancies (in this case, expression of PAX8 and Thyroglobulin can help distinguish metastatic thyroid carcinoma from primary pulmonary adenocarcinoma)(21, 22).

80% of lung adenocarcinomas are positive for Napsin A, which can be applied to differentiate adenocarcinoma from squamous cell carcinoma. Napsin A is an aspartic proteinase expressed in proximal and distal renal tubules and normal type 2 pneumocytes; its positivity in 80% of lung adenocarcinomas can be used together with TTF1 to identify adenocarcinomas.

An IHC panel of TTF-1 (or Napsin A) and p40 (or p63) may be sufficient for a small biopsy specimen to refine the diagnosis of either adenocarcinoma or squamous cell carcinoma. If the primary origin of the carcinoma is uncertain, the pathologic evaluation should also include an IHC panel to rule out metastatic carcinomas. Usually, a limited panel of IHC markers is used to evaluate for NSCLC; then, this proceeds to additional IHC markers to evaluate possible metastasis from other sites.

Other Immunomarkers that may be useful to assess for metastatic carcinoma to the lung include ERα, PR, GCDFP-15, mammaglobin, GATA-3 for breast carcinoma, PAX8, PAX2, ER for ovarian papillary serous carcinoma, PAX8 for renal cell carcinoma, CDX2 for gastrointestinal carcinoma or NKX3.1 for prostate carcinoma.

Small cell lung carcinoma is positive for TTF-1 and negative for p63 & CK 34βE12. Markers of neuroendocrine differentiation are usually positive in small cell lung carcinoma, including CD56/NCAM, insulinoma-associated protein 1 (INSM1), synaptophysin and chromogranin. The

confirmatory IHC staining is useful when morphologic features of neuroendocrine differentiation are identified.

1.6 Staging in lung cancer

Stage classification is an essential and fundamental part of cancer diagnosis and treatment. It provides a nomenclature to describe the tumor's anatomic extent, which strongly correlates with patients' outcomes and plays a significant role in selecting therapeutic options It is also critical for clear communication between cancer researchers in discussions and when comparing the results of clinical trials.

The fundamental part of stage classification is the TNM system; T is for primary tumor characteristics, N is for nodal involvement, and M is for metastasis. Specific T, N and M categories exhibit similar behavior, which can be classified as stage groups. Two organizations define the TNM: American Joint Commission on Cancer (AJCC) in the United States and Union for International Cancer Control (UICC) internationally. Lung cancer is unique concerning staging classification since it is based on a statistical analysis of an international database of more than 100,000 patients (23).

The above analysis (23, 24)and other publications (24-29) address the T, N and M and stage groups in Non-small Cell lung cancer patients. The methodology and validation methods of the above findings are also described in the series of articles published in the Journal of thoracic oncology. The current staging for lung cancer was developed based on these analyses. The current staging is illustrated below in tables 1.1 and 1.2. It is essential for both clinicians and researchers to be informed about the latest staging system.

As mentioned above, the availability of a large dataset promotes greater granularity allowing us to describe more specific tumor characteristics. Moreover, it provides a tool to define treatment for more specific subgroups of patients.

Table1.1 Staging of non-small cell lung cancer (AJCC 8th edition) (11)

T (Primary Tumor)	
T0	No primary tumor
Tis	Carcinoma in situ
T1	≤3cm
T1mi	Minimally invasive adenocarcinoma
T1a	Superficial spreading tumor in central airways
T1a	Tumor≤1cm
T1b	Tumor >1 but ≤2cm
T1c	Tumor >2 but ≤3cm
T2	Tumor >3but ≤5cm or tumor involving visceral pleura, main bronchus (not carina), atelectasis to hilum
T2a	Tumor >3but ≤4cm
T2b	Tumor >4 but ≤5cm
T3	Tumor >5cm but ≤7cm or invading chest wall, pericardium, phrenic nerve or separate tumor nodule in the same lobe
T4	Tumor>7 cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe
N (Regional Node)	
N0	No regional node metastasis
N1	Metastasis in ipsilateral pulmonary or hilar nodes
N2	Metastasis in ipsilateral mediastinal or subcarinal nodes
N3	Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes
Metastasis (distant metastasis)	
M0	No distant metastasis
M1a	Malignant pleural or pericardial effusion or pleural or pericardial nodules or separate tumor nodules(s) in a contralateral lobe
M1b	Single extra-thoracic metastasis
M1c	Multiple extra-thoracic metastases (1 or>1 organ)

Table 1.2 AJCC prognostic group (11)

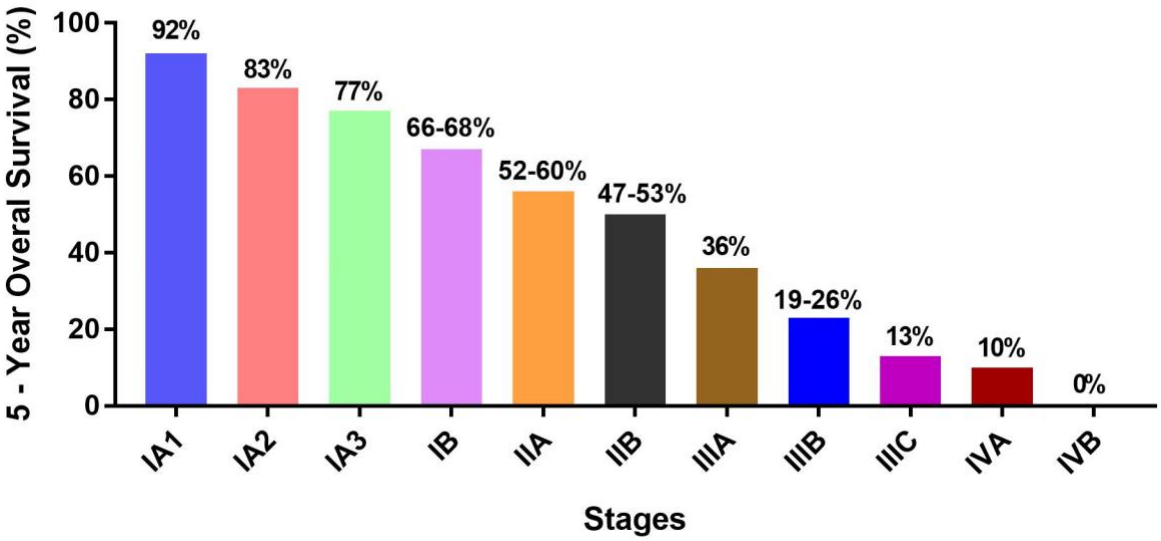
T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

1.7 Survival statistics

The long-term survival of lung carcinoma remains poor, with limited improvement having been made in recent years in long-term survival rates. In a review of data from the United States collected in the SEER program, 1-year survival rates had increased from 34.4% in 1975–1977 to 44.7% in 2006–2009. The 5-year survival rate is 53.5% for cases detected when the disease is still localized, 26.1% for patients with regional disease, and 3.9% for patients with distant metastases (30).

Lung cancer survival decreases rapidly with increasing stage. Figure 1.3 depict the survival results of lung cancer patients developed by IASLC project (23),(31) , which collected survival data of lung cancer patients worldwide, including in Canada.

Figure 1.3 Five-year survival of NSCLC patients based on IASLC staging study (adopted from Rami-Porta et al (2014) (23)



1.8 Molecular biomarkers in lung cancer

Molecular testing is used for oncogenic genomic driver events for which targeted therapies are available. It is mainly used for advanced metastatic disease. Nevertheless, testing for specific biomarkers is also recommended for some early-stage and locally advanced NSCLC.

The tiered KRAS testing approach is acceptable based on the low prevalence (3-5%) of co-occurring biomarkers.

Broad molecular profiling systems may be used to test for multiple biomarkers simultaneously. Next generation sequencing (NGS) is a broad molecular profiling system that can detect panels of mutations and gene fusions if the NGS platforms have been designed and validated to detect these somatic genomic alterations. ROS1 and ALK gene rearrangements can be detected using fluorescence in situ hybridization (FISH), NGS, and other methods. The section below will explore some of the more common genetic changes associated with NSCLC.

1.8.1 ALK Gene Rearrangements

ALK gene rearrangements occur in about 5 % of cases (32). Like patients with EGFR mutation, patients with this type of genetic change are usually nonsmokers or nonheavy smokers. This genetic change is more common with adenocarcinoma. ALK gene rearrangement patients are usually resistant to tyrosine kinase inhibitors (TKI). Brigatinib (33), crizotinib (34-36), ceritinib ,alectinib (35) or lorlatinib (34) are the drugs used for these patients. Patients with squamous cell carcinoma have a lower rate of ALK rearrangements than patients with adenocarcinoma.

Usually, diagnostic FISH testing is used for the evaluation of ALK rearrangement. IHC testing can also be used as a prescreening test.

1.8.2 BRAF V600E Mutations

BRAF (v-Raf murine sarcoma viral oncogene homolog B) is a serine/threonine kinase part of the MAP/ERK signalling pathway.

The BRAF V600E mutation occurs in about 2% of patients with lung adenocarcinoma.

This type of mutation is the targetable mutation for BRAF. Smoking history is usually more prominent in patients with BRAF V600E mutation compared to patients with ALK or EGFR mutation, who are usually light or nonsmokers.

Metastatic NSCLC patients can be considered for BRAF mutation testing. Different agents have been approved for the treatment of BRAF mutant metastatic NSCLC. BRAF p.V600E mutant patients can be treated with a combination of trametinib and dabrafenib. Single-agent treatment with dabrafenib or vemurafenib is also used. Chemotherapy is also an option depending on the circumstances.

1.8.3 EGFR Mutations

Testing for EGFR mutations has importance, especially in metastatic NSCLC patients.

In the resectable stage (IB to IIIA NSCLC), molecular testing can help to determine if adjuvant therapy with osimertinib is warranted. EGFR mutation is usually associated with two common changes; a deletion in EGFR Exon 19 (in 45% of cases); a point mutation in Exon 21 (in 40% of cases). Both mutations lead to activation of the tyrosine kinase domain, resulting in sensitivity to EGFR tyrosine kinase inhibitors. Gefitinib, erlotinib, osimertinib afatinib and dacomitinib are among the common tyrosine kinase inhibitors used to treat patients with EGFR mutation.

Some fewer common mutations account for approximately 10% of cases, which are also sensitive to EGFR TKIs, including exon 19 insertions, p. L861Q, p. S768Iand/or p. G719X. Only patients with these mutations are sensitive to treatment with TKI and subsequently would benefit from therapy with these agents.

The phenotype of patients harboring EGFR mutation is a nonsmoker or light smoker patient with adenocarcinoma histology. Although EGFR mutation is not common in squamous cell carcinoma histology, guidelines have advocated testing for EGFR mutation in patients with metastatic squamous cell carcinoma.

EGFR tyrosine kinase inhibitors are used as first-line treatment in patients with EGFR mutations in a metastatic state. Different studies evaluated the role of EGFR inhibitors versus common chemotherapy agents. Afatinib was compared with cisplatin plus pemetrexed in metastatic adenocarcinoma, and patients' progression-free survival (PFS) was longer with afatinib (11.1 Vs 6.9)(37). Erlotinib was compared with cisplatin/carboplatin plus gemcitabine, which showed the superiority of erlotinib in the study. The PFS was 9.7 months with erlotinib, and it was 5.2 months with chemotherapy (Cis/Carbo plus gem) (38). Gefitinib was compared with cisplatin plus docetaxel, and the PFS was superior (9.2 Vs 6.3) (39) Overall survival analysis for afatinib showed no superiority of this TKI when compared with chemotherapy (40). Outstandingly, a small subset of patients with EFGR mutation with deletion of exon 19 showed benefits in survival with this agent.

BRAF and KRAS mutations and ALK or ROS1 gene rearrangements are usually associated with unresponsiveness to EGFR targeting agents.

Most patients with the common EGFR mutations eventually become resistant to erlotinib or afatinib; usually, the range for PFS is about 9 to 13 months.

EGFR Thr790Met (T790M) is a mutation associated with acquired resistance to EGFR TKI therapy and has been reported in about 60% of patients with disease progression after initial response to erlotinib, gefitinib, or afatinib. Usually, resistance to TKI happens through mutation in EGFR Thr 790 Met.

Resistance to EGFR TKIs may be associated with small cell histology. Other molecular events, such as the acquisition of ALK rearrangement, HER2 amplification or MET, and other biomarkers, can also mediate acquired resistance.

IHC is not recommended for detecting EGFR mutations. PCR testing Next Generation Sequencing is a method used to assess EGFR mutations.

EGFR-positive metastatic NSCLC can be treated with Osimertinib. Other possible agents are erlotinib, afatinib, gefitinib and dacomitinib. Erlotinib plus bevacizumab can also be used. Bevacizumab should not be prescribed in patients with squamous pathology or hemoptysis history. Osimertinib is recommended as secondary therapy for patients with EGFR T790M–positive metastatic NSCLC who progressed on previous agents (like erlotinib and afatinib).

The treatment of metastatic NSCLC is beyond the scope of this writing, especially in the second and third lines of treatment.

1.8.4 KRAS Mutations

KRAS is a G-protein with GTPase activity that is part of the MAP/ERK pathway; point mutations in KRAS usually occur at codon 12.

About one-fourth of adenocarcinoma patients harbour KRAS mutation. Unlike other mutations, KRAS mutation is usually associated with heavy smoking. As mentioned above, KRAS is a prognostic factor, as patients with this type of mutation usually die earlier compared to patients

without this mutation. Also, patients with KRAS mutation do not respond to EGFR TKI. On the other hand, patients with this type of mutation have a similar response to chemotherapy agents. Given that this mutation usually does not coexist with other mutations, it seems appropriate to evaluate KRAS mutation at first steps when approaching patients for actionable mutation since a positive test can prevent further testing.

Single-agent Immune checkpoint inhibitors are effective in 25% of KRAS-positive metastatic NSCLC (41).

1.8.5 MET Genomic Alterations

C-MET, the hepatocyte growth factor (HGF) receptor, is a tyrosine kinase receptor involved in cell survival and proliferation; genomic alterations in MET that cause mutation include METex14 skipping mutations, MET gene copy number (GCN) gain or amplification, and MET protein overexpression. The type of mutation is important as it may dictate the treatment type. METex14 skipping mutations and MET amplification may occur together. It should be noted that MET mutational changes usually do not occur with other mutations.

3% to 4% of adenocarcinoma patients and 1% to 2% of patients with other histology may have METex14 skipping mutation. The most common phenotype of METex14 skipping mutation is in nonsmoker female patients. Next Generation Sequencing is usually used for detecting METex14 skipping mutations. RNA-based NGS may have improved detection. IHC is not used in the detection of this type of mutation. There is only a response to checkpoint inhibitors in 16% of cases with METex14 skipping mutation, even in PDL1 positive patients with higher positivity.

Additionally, patients with MET amplification respond better to immunotherapy. Currently, tepotinib or capmatinib are recommended treatments for patients with METex14 skipping mutation. Other possible treatments include crizotinib or chemotherapy agents.

1.8.6 NTRK1/2/3 Gene Fusions

NTRK gene fusions encode tropomyosin receptor kinase (TRK) fusion proteins.

NTRK1/2/3 fusions happen in 0.2% of NSCLC, and like other mutations, there is usually no overlap with other mutations. Detection methods are Next Generation Sequencing, FISH, and PCR assays. Larotrectinib and entrectinib are two possible treatments for patients with NTRK gene fusion.

1.8.7 RET Rearrangements

RET is a tyrosine kinase receptor that affects cell proliferation and differentiation. Rearrangements may occur in NSCLC between the RET gene and other domains, especially kinesin family 5B (KIF5B) and coiled-coil domain containing-6 (CCDC6), which lead to overexpression of the RET protein (42, 43).

RET rearrangements occur in about 1% to 2% of patients with NSCLC. RET rearrangements may infrequently overlap with other mutations like EGFR or KRAS mutations. Next-generation sequencing, FlSH, and RT-PCR are usually used to detect RET rearrangements. NGS has high specificity for the detection of RET mutations.

Single-agent ICIs are effective in 6% of patients with RET mutation. Cabozantinib is another agent that is used for the treatment of patients with RET mutations.

1.8.8 ROS1 Rearrangements

ROS1 is a receptor tyrosine kinase with similarities to ALK and insulin receptor family. ROS1 gene rearrangements are positive in 1% to 2% of patients with NSCLC. Crizotinib, ceritinib, and entrectinib are useful in patients with ROS1 rearrangements (44),(45). ROS1 testing should be part of the patient's evaluation with metastatic squamous cell carcinoma; still, the prevalence of this mutation is lower than in non-squamous patients. crizotinib, entrectinib, or ceritinib are options in patients with ROS1 mutation with metastasis.

Systemic chemotherapy is also an option for adenocarcinoma or squamous cell carcinoma patients with these mutations.

1.9 Immune Biomarkers in lung cancer

1.9.1 PD-L1 Expression Levels

Human Immune checkpoint inhibitors are antibodies inhibiting the PD-1 receptor or PD-L1, which will improve antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells. Pembrolizumab, Nivolumab, and cemiplimab inhibit PD-1 receptors. Atezolizumab and durvalumab inhibit PD-L1 (46, 47).

All metastatic NSCLC patients should be evaluated for PD-L1 expression. PD-L1 expression is the sole test for assessing whether a patient can benefit from PD-1 or PD-L1 inhibitors.

An important issue about PD-L1 expression is that the expression may change during the treatment.

Testing for PD-L1 is not required for prescribing first-line therapy with specific Immune Checkpoint inhibitor regimens, for example, cemiplimab monotherapy or atezolizumab with or

without chemotherapy or if treatment is used subsequent therapy with single-agent nivolumab or atezolizumab.

It is recommended that molecular testing should be obtained before administering Immunotherapies. Molecular testing recommended are ALK, BRAF, EGFR, METex14 skipping, NTRK1/2/3, RET, and ROS1 variants. If molecular testing is not done, patients should be treated as not having any mutations.

Patients with metastatic NSCLC and PD-L1 expression of 1% or more and targetable mutation should be first treated with the targeted therapy because of the higher response rate associated with targeted therapy. Osimertinib response rate is around 80% in the first line setting, and the checkpoint inhibitor response rate is lower.

1.9.2 Total mutational burden

The total mutational burden is an approximate measure of the number of somatic mutations, typically high in the smoker or former smoker NSCLC patients (Low TMB is more commonly detected in non-smokers). Studies have suggested that TMB might be a useful immune biomarker for decision-making. It can be used to decide if a patient would benefit from Immunotherapy. On trial, patients had survival benefits regardless of PD-L1 expression or mutational burden (48). Different studies did not show any added benefit when mutation burden is added to the PD-L1 expression level.

Other problems associated with total mutational burden are the need for standard cut-off points between high and low and the lack of consistency between labs concerning measurement. All the factors mentioned above make PD-L1 expression better tested when predicting immune therapy response.

1.10 Local treatments for NSCLC

1.10.1 Radiation therapy

Radiation therapy has a role in every stage of NSCLC patients. The role of radiation therapy can be classified into three major classes: definitive treatment, palliative treatment and adjuvant or neoadjuvant treatments after or before surgery. The first class includes definitive treatments of patients with lung cancer stage I and II and definitive chemoradiation of stage III patients. Palliative treatments have a role in patients with recurrence or metastatic patients. Also, radiation can be a palliative treatment modality in patients with incurable cancers. Radiation therapy can also be used in the preoperative or postoperative setting (49, 50). The goal of treatment with radiation is to provide a cure when used as definitive therapy and to provide palliation when used in the palliative setting. When delivering radiation, regardless of its combination with radio-sensitizing agents (e.g., platinum agents), some basic properties should be followed.

There have been advancements in radiation delivery technologies during the last two to three decades. Radiation therapy has been revolutionized with the introduction of 4D-conformal RT and simulation, Intensity-Modulated RT/volumetric modulated arc therapy (IMRT/VMAT), image-guided radiation therapy (IGRT) and motion control modalities.

These changes are apart from the institution of Stereotactic Ablative Radiotherapy, which has truly changed the face of lung cancer treatment. Stereotactic radiotherapy will be discussed in another section. As discussed in more detail in the second chapter of this writing, improvement in radiotherapy is one of the significant developments in recent decades. The improvement in radiotherapy dose and dose per fraction, in combination with other enhancements, has led to

survival benefits that we can observe in stage I and II lung cancer patients. There has been upgrading in the conventional radiotherapy regimes as well; conventional radiotherapy is used in patients with stage III locally advanced lung cancer patients in combination with radiosensitizers. The radiation simulation procedure involves 4D CT scanning. The simulation is performed with the immobilization devices and in the treatment position.

When the 4D CT scan is applied, it usually divides respiration into 10 phases. CT images are taken, and the CT images are sorted for each phase. Depending on the phase of respiration, the full inspiration is 0% which is the time the diaphragm is down (flat shaped and in contraction), and there is 60% which correlates with maximum expiration, when the diaphragm is up (dome-shaped and in relaxation). CT scan images are then labelled based on the phase of respiration.

Radiotherapy for early-stage lung cancer patients is beyond the scope of this thesis, but usually, Stereotactic radiation is the preferred method of radiation in early-stage lung cancer patients.

SBRT can be safely used in high surgical risk patients like the elderly or patients with poor lung function.

1.10.2 Surgery

Surgery can be applied to patients with early-stage lung cancer. One of the main problems associated with NSCLC cancer is that the median age of NSCLC patients is 71 years old; usually, a significant proportion of patients are medically inoperable. If the tumor seems resectable, then the surgical procedure depends on the tumor's extent and the patient's cardiopulmonary reserve.

A preoperative or intraoperative tissue diagnosis is recommended before the definite surgical intervention. Lobectomy, bilobectomy or pneumonectomy can be done after obtaining tissue.

Lung-sparing procedures are preferred over pneumonectomy. The most critical part of the surgery is achieving negative margins. Anatomic pulmonary resection is usually preferred in most NSCLC patients. Sublobar resection segmentectomy and wedge resection should achieve a margin of more than or equal to 2 centimeters or more than the nodule size. Sublobar resection should be accompanied by a sampling of N1 and N2 lymph node stations. Segmentectomy can be done for patients with peripheral nodules less than 2 cm if the pathology is pure Adenocarcinoma in situ or nodule has more than 50% ground glass appearance or if the radiology shows that there is a long doubling time (more than 400 days). Medically inoperable patients can be referred for radiotherapy in stages I and II.

Lymph node dissection

Darling et al. aimed to determine if survival outcomes are improved by mediastinal lymph node dissection (MLND) compared to mediastinal lymph node sampling (MLNS) in T1 or T2 NSCLC patients undergoing resection for N0 or non-hilar N1. In this study, patients with early-stage lung cancer with negative node sampling by systematic dissection and complete mediastinal lymph node dissection did not improve survival (51). Systematic lymph node sampling should be done during pulmonary resection. For left-side cancers, 4L,5,6,7,8 and 9 should be sampled. 2R,4R,7,8 and 9 should be sampled for right-sided cancers. Patients undergoing resection for stage IIIA (N2) should have mediastinal lymph node dissection on the ipsilateral side.

Thoracoscopic resection

Video-assisted thoracic surgery (VATS) is a minimally invasive procedure that will shorten hospital stays and improve patient quality of life. Less pain is expected with these procedures. The

oncologic outcomes are acceptable and postoperative mortality and morbidity are lower. Intraoperative bleeding is lower with this procedure. As mentioned above, stage I NSCLC patients have acceptable oncologic outcomes with thoracoscopic lobectomy. Specifically, the 5-year survival rate and local recurrence rate were satisfactory(52).

Surgery has a role in treating patients with stage IIIA(N2) disease. Regardless, careful staging of these patients has great importance. It is essential to use radiologic and invasive staging to document the disease in these patients. It should be noted that based on randomized trials, surgery does not prolong the survival of patients with IIIA(N2) disease. Patients with multiple pathologically proven malignant nodes greater than 3 cm are not good candidates for surgery, and chemoradiation is the preferred treatment method in these patients. Surgery can be used in selected N2 patients that responded favourably to induction chemotherapy. Neoadjuvant chemoradiation is also another alternative to neoadjuvant chemotherapy.

Chapter II

Contributions of chest radiotherapy and adjunct therapies in the unresected Locally Advanced Non-Small Cell Lung Cancer (LA-NSCLC) outcomes.

Current standard of care - Open Questions.

2.1 Introduction

Most patients with locally advanced lung cancer are inoperable and a significant number of patients who present with inoperable LA-NSCLC receive palliative care. The treatment goals in this setting are to relieve pain and other symptoms and improve or maintain the quality of life. Until the 1990 s, RT alone was the standard treatment for patients with inoperable NSCLC; however, the 5-year survival rate was poor (under 10%) (53). As the survival of patients with RT alone was poor, efforts were made to expand the outcome of these patients with the addition of chemotherapy. The initial trials had conflicting results. Trovo et al. (54) compared RT versus RT with low-dose cisplatin, which showed a non-significant difference in the patient's outcomes (Median Survival 10.3 Months Vs 9.97 Months).

Morton et al. (55) compared RT with chemoradiation (CRT) in a phase 3 trial; patients' outcomes were similar, two-year survival was 16% versus 21% in RT versus CRT, and 5-years survival was 5% versus 7%, respectively. Similarly, Mattson et al. (56) failed to show any improvements in the outcome of CRT patients.

Over the last three decades, a few studies(57-60) have demonstrated that CRT and RT can prolong survival, and combination therapy evolved as a treatment for locally advanced diseases. The combination of RT plus platinum-based chemotherapy for LA-NSCLC showed survival benefits and is now considered standard of care. Combination therapy can be given concurrently or sequentially. The superiority of chemotherapy plus RT was first proved in sequential trials(57, 58, 60). Concurrent chemotherapy’s advantage was demonstrated in subsequent trials(61, 62).

Concurrent chemoradiation (cCRT) is the standard of care for medically fit unresectable LA-NSCLC patients.

2.1.1 Addition of chemotherapy to RT

2.1.1.1 Sequential chemotherapy trials

Integration of chemotherapy with radiation was explored in different trials. Dillman et al. (57) published one of the first trials that compared sequential CRT with RT alone. This trial used stringent eligibility criteria, requiring excellent performance status, minimal weight loss, and visible disease in radiographic evaluations. The addition of chemotherapy provided benefits with a median survival of 13.8 months compared to 9.7 months with RT alone (26% vs 13% after 2 years and 17% vs 6% after 5 years for overall survival (OS)). However, the rate of severe complications and weight loss also increased to 7% and 14% with CRT vs 6% and 3% in RT alone group. Similarly, Le Chevalier et al. (58) enrolled similar patients and reported a marginal but statistically non-significant difference in OS (21% with CRT vs 14% with RT at 2 years). Sause et al. (59) tested the same concept and added a third arm of hyper-fractionated radiotherapy. This trial showed a slight survival advantage with a median OS of 13.2 months for CRT vs 11.4 months for RT. Interestingly, in patients over 70 years of age, the survival benefit was in the standard RT alone arm. All toxic deaths secondary to chemotherapy were reported in patients >70 years of age. Furthermore, Schaake-Koning et al. (60) compared the survival benefit of low-dose daily cisplatin with RT vs RT alone. This trial failed to show superiority with weekly cisplatin. The Sequential chemotherapy radiotherapy trials are summarized in table 2.1.

Table 2.1 Sequential chemotherapy radiotherapy trials

Ref	Study (year)	Median Survival (CRT vs RT) Months	Chemotherapy agent	2Years OS (CRTvs RT)	RT dose Total /	# Patients
(57)	Dillman, (1990)	13.8 vs 9.7	Cisplatin+Vinblastin	26% vs 13%	60Gy	155
(58)	Le Chevalier (1991)	12 vs 10	Cisplatin+vindisin+ Cyclophosphamide+ Lumostin	21% vs 14%	65 Gy	353
(59)	Sause (2000)	13.2 vs 11.4	Cisplatin+Vinblastin		60 Gy	458
(60)	Caro Shaake (1992)	13 Vs 12	Cisplatin weekly Cisplatin daily	26% vs 13% Daily cis vs RT	55Gy	331

2.1.1.2 Concurrent chemotherapy trials

The concurrent CRT (cCRT) role was established after its proven superiority over sequential treatment. One of the first trials that compared cCRT with sequential treatment was conducted by Furuse et al. (62) in 1999. In this trial, 321 patients were evaluated, and the concurrent arm showed superiority in median survival (16.5 months Versus 13.3 months). The 2 Years survival benefit was 34.6 % vs 27.7 %. Five years of survival for the concurrent arm was 15.8% versus 8.9 % in the sequential arm.

Curran et al. (61) evaluated the role of cCRT versus Sequential treatment in 2011. In the RTOG 9410, Curran evaluated the cCRT regime with sequential treatment in a trial involving three arms. The first arm included sequential chemotherapy with cisplatin and vinblastine and radiation later,

and the second arm used the same chemotherapy regime concurrently with radiation. The third arm used cisplatin and etoposide with hyper-fractionated RT. Median survival was 14.6 months in the sequential arm and 17 months in the concurrent arm; surprisingly, the median survival was 15.6 months in the hyper-fractionated CRT arm. 5year Overall survival was 10%, 16% and 13%, respectively. The Concurrent chemoradiation trials are summarized in table 2.2.

Table 2.2 Concurrent chemoradiation trials

ref	Study (year)	Study arms	Patients Number	RT dose	Median survival	5y OS	Response Rate
(61)	Curran (2011)	1)Cisplatin +Vinblastine seq 2)same chemotherapy CC 3)Cisplatin + Etoposide	611	1)60Gy 2)60 Gy 3)69.6 Gy	1)14.6 2)17 3)15.6	1)10% 2)16% 3)13%	1)70% 2)61% 3)65%
(62)	Furuse (1999)	1)cisplatin +Vindesin+ mitomycin CC 2)same regime seq	320	56 Gy	1)16.5 2)13.3	1)15.8% 2)8.9%	1)84% 2)66%

2.1.1.3 Chemoradiation in the elderly

The role of concurrent chemoradiation in the elderly was evaluated by Atagi et al. (63). Atagi evaluated the role of CRT in 200 stage 3 patients who were more than 71 years old. One hundred patients were allocated to chemoradiation, and one hundred patients were allocated to radiation alone. The median age of patients in this trial was 77 years old. This phase 3 trial was run by the Japan Clinical Oncology Group (JCOG 0301) and published in 2012. The chemotherapy regime used was Low dose carboplatin (30 mg/m2) in combination with radiation. All of the patients received a radiation dose of 60 Gy in 30 fractions. This trial showed a survival advantage in the CRT group. Median survival was 22.4 months in the cCRT arm versus 16.9 months in RT alone

arm. The 2 years overall survival was 46.3% vs 35.1%, which showed a statistically significant advantage in the CRT group.

Table 2.3 Chemoradiation in elderly patient trial

ref	Study (year)	Study arms	RT dose	Median survival	2y OS
(63)	Atagi (2012)	Chemoradiation with Low dose Carboplatin Vs Radiation alone	60Gy/30F	22.4 Months Vs 16.9 Months	46.3% Vs 35.1 %

2.1.1.4 Pitfalls associated with concurrent chemoradiation (cCRT)

Although evidence of the advantage of multimodal treatment consisting of chemotherapy with RT is present, essential points need attention. First, chemotherapy trials used stringent inclusion criteria like age, weight loss of less than 10%, and good performance status, which makes extrapolation of their results to all LA-NSCLC patients challenging. The average age of a lung cancer patient is reported to be 71 years (64) which means that most patients are elderly patients. Generally, population-based studies show that less than 30% of LA-NSCLC patients eventually receive RT, which is a strong indicator that the majority of this group of patients were out of the eligibility criteria set for the cCRT trials. Second, 66% - 76% of patients with LA-NSCLC have at least one concurrent medical condition (65, 66), and patients with comorbidities are often not included in trials. Third, during the last three decades, the advantages of sequential and Concurrent chemoradiation were demonstrated for stage III patients. However, the optimal chemotherapy regimen is unknown, with some different platinum doublets being used in studies from the 1990s. Recent gains in managing stage IV NSCLC have not translated to benefits in managing stage III

disease. For example, despite the superiority of pemetrexed with cisplatin in the management of metastatic non-squamous NSCLC (67), a study of nonmetastatic disease failed to show the superiority of the same regimen over etoposide/cisplatin when given concurrently in stage III non-squamous disease (68). Furthermore, tyrosine kinase inhibitors successfully used in stage 4 disease against genetic targets, such as epidermal growth factor receptor (EGFR), are not used in stage III, regardless of the driver mutation. Therefore, most centers are using the same regimens that have barely changed over the last 30 years. In stage III NSCLC, cCRT is currently given on a 'one size fits all basis despite significant proven variability in clinical and pathological features of this broad group of patients.

Increased toxicity, especially with concurrent treatment, is another point warranting consideration. Acute toxicities, including esophagitis, radiation pneumonitis, and chemotherapy-specific adverse events, are among the most prominent problems. In RTOG 94-10 trial (61), which was discussed above, grade 3 esophagitis was 4% in the sequential arm but increased to 22% in the concurrent once-daily RT arm. Acute radiation Pneumonitis is rarely an issue, but most commonly, radiation pneumonitis manifests 6 months after treatment. However, with the current advancement in radiation delivery, the risk of this side effect has been reduced considerably.

Hematologic toxicities are another problem associated with concurrent treatment; since chemotherapy is a form of systemic therapy, it carries risks of separate toxicities. Principally, hematologic toxicities (granulocytopenia, anemia, thrombocytopenia, and leukopenia) can compromise the receipt of further chemotherapy (or RT) and may impact outcomes. In RTOG 94-10 (61), the overall rate of grade 3 thrombocytopenia, leukopenia and granulocytopenia was 10%, 70% and 71%, respectively.

2.2 Attempts to improve the Contribution of Radiotherapy

2.2.1 Efforts to dose escalate

The radiation dose which is used in patients with stage III NSCLC, is based on studies that established it almost 30 years ago (53). Different investigators run various trials to evaluate the effects of dose escalation in Stage III lung cancer patients, with the aim of increasing locoregional control rate and overall survival. Phase 1 and phase 2 trials were designed to establish the safety and efficacy of the increasing total dose while reducing the irradiated volume with the aid of three-dimensional Radiotherapy or Intensity-modulated radiotherapy (69, 70) (71-74).

Findings from these trials were similar, showing that a maximum tumor dose of 74 Gy given with concurrent weekly paclitaxel and carboplatin was safe and resulted in median overall survival of roughly 24 months versus a median overall survival of 17.1 months in patients given a 60 Gy dose in RTOG 9410 (61).

RTOG 0617 was the phase 3 trial that compared dose escalation in patients with stage III NSCLC(75). This trial was designed to compare the overall survival of patients with stage 3 non-small cell lung cancer after standard dose versus high dose conformal radiotherapy with cCRT and the addition of cetuximab to cCRT. RTOG 0671 had 4 arms; 544 patients were randomized to standard cCRT (60Gy), high-dose cCRT (74Gy), standard cCRT with cetuximab and high-dose cCRT with Cetuximab. The survival was 28.7 Months for standard cCRT and 20.7 Months for high-dose cCRT. Median OS was 25 months for the group receiving cetuximab versus 24 months for those not receiving cetuximab. It was interpreted that 74Gy radiation given in 2Gy fractions

with concurrent chemotherapy was not better than 60Gy plus concurrent chemotherapy for patients with stage III non-small-cell lung cancer and might be potentially harmful. Adding cetuximab to cCRT and consolidation treatment provided no benefit in overall survival for these patients.

Table 2.4 dose escalation trials for stage III NSCLC

Ref	Study(year)	Study arms	Chemotherapy agent	N patients	Median OS	Radiation Dose
(76)	Bradly (2015)	A) standard Chemoradiation	A) Carboplatin+ paclitaxel	A)166	A)28.7	A)60
		B) High-Dose Chemoradiation	B) Same	B)121	B)20.7	B)74
		C)ST-CRT +Cetuximab	C)Same	C)147	C)25	C)60
		D)HD-CRT +Cetuximab	D)same	D)110	D)24	D)74

2.2.2 Modern RT Modalities

Intensity-modulated radiation therapy (IMRT) and three-dimensional conformal EBRT (3D-CRT) have not been compared prospectively in treating LA-NSCLC patients. Dosimetric studies have shown that IMRT reduces the delivered doses to the nearby tissues (such as lungs, esophagus, and heart), by improving conformity of the RT dose distribution. A retrospective MD Anderson Cancer Center study compared IMRT with 3D-CRT and found that IMRT provides equivalent survival to 3D-CRT despite that IMRT patients had significantly worse performance status and larger tumors (77). Chun et al. (78) performed a secondary analysis to compare IMRT with 3D-CRT in NRG

Oncology clinical trial RTOG 0617 patients; 53% of patients were treated with 3D-CRT and 47% with IMRT. The IMRT group had larger planning treatment volumes (median, 427 v 486mL; P = 0.005); a larger planning treatment volume/volume of lung ratio (median, 0.13 v 0.15; P = 0.013); and more stage IIIB disease (30.3% v 38.6%, P = 0.056). Two-year OS, progression-free survival, local failure, and distant metastasis-free survival were not different between IMRT and 3D-CRT. IMRT was associated with less grade 3 pneumonitis (7.9% v 3.5%, P = 0.039) and a reduced risk in adjusted analyses (odds ratio, 0.41; 95% CI, 0.171 to 0.986; P = 0.046). IMRT also produced lower heart doses (P, 0.05), and the volume of the heart receiving 40 Gy (V40) was significantly associated with OS on adjusted analysis (P<0.05). The lung V5 was not associated with any grade 3 toxicity, whereas the lung V20 was associated with increased grade 3 pneumonitis risk on multivariable analysis (P = 0.026). In conclusion, IMRT was associated with lower rates of severe pneumonitis and cardiac doses in NRG Oncology clinical trial RTOG 0617, which supported routine use of IMRT for locally advanced NSCLC.

2.2.3 Heart sparing - Heart dose

In the RTOG 0617, heart dose was proved to be a contributing factor to the Overall survival (76); in fact, it was presumed to be the underlying cause of the lower overall survival in the high dose chemoradiation group. Although the relationship was proven, the report has not established actionable parameters.

Speirs et al. (79) evaluated the clinical and dosimetric factors affecting the survival of LA-NSCLC patients with a focus on heart dose. A total of 416 patients with LA-NSCLC were evaluated. Patients were treated with radiation therapy at prescribed doses of 50.0 to 84.9 Gy (median 66.0 Gy). Median OS was 16.8 months. The 1- and 2-year OS rates were 61.4% and 38.8%,

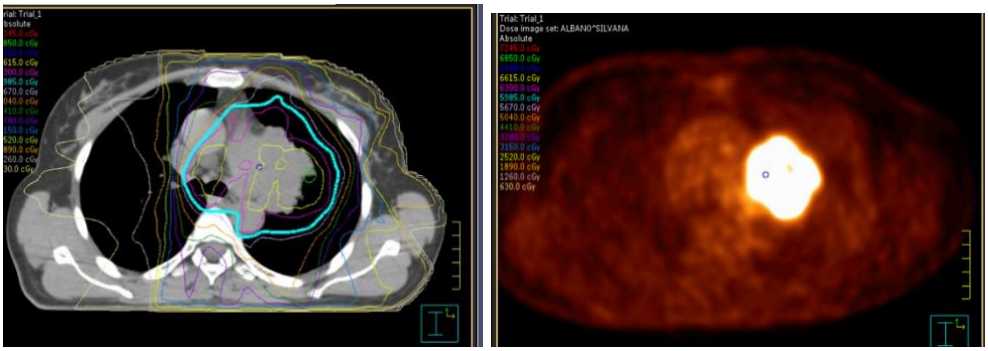
respectively. On multivariate analysis, factors independently associated with worse OS were increasing heart V50, heart volume, lung V5 (proportion of the lung structure [excluding the target volume] receiving at least 5 Gy), bilateral mediastinal lymph node involvement, and lack of concurrent chemotherapy. When stratified by heart V50 less than 25% versus 25% or greater, the 1-year OS rates were 70.2% versus 46.8%. 2-year OS rates were 45.9% versus 26.7%. Median heart V50 was significantly higher (20.8% versus 13.9%) for patients with cardiac toxicity.

2.3 Fluorodeoxyglucose (FDG)-positron emission tomography (PET) FDG - PET

2.3.1 Impact of modern staging – stage migration

Staging has evolved through the introduction of positron emission tomography (PET), brain MRI, and mediastinal staging with endoscopic ultrasound guidance (80). Treatment delivery has improved in different aspects; with the integration of PET into treatment planning at the primary tumor level, PET can potentially decrease the gross tumor volume (GTV) when there is especially atelectasis associated with the tumor. At the nodal level, it can affect nodal volume by further highlighting involved areas. The effect of PET integration with tumor delineation has been studied in multiple studies (81-86). For patients diagnosed with NSCLC, positron emission tomography with 18Fluorodeoxyglucose (FDG-PET) can serve various purposes.

Figure 2.1 Effect of PET in tumor delineation



2.3.2 Staging and stage migration

Adding PET to the workup of potentially operable patients upstages approximately 20% of patients and reduces the rate of futile thoracotomies (87). PET findings may lead to a change plan in many patients being considered for definitive CRT (88).

2.3.3 Metabolic Tumor Volume

ACRIN RTOG 0235 was a prospective, multi-institutional trial performed to evaluate the prognostic value of pre- and post-treatment PET imaging for patients treated with definitive cCRT for stage III and medically inoperable stage II NSCLC (89). Patients with stage III NSCLC underwent FDG-PET prior to treatment. In this trial, a commercially available gradient-based segmentation tool was used to contour all visible hypermetabolic lesions on each scan. For each patient in the study, the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total glycolytic activity (TGA) for all contoured lesions were recorded. In multivariable analysis incorporating clinical and imaging data available prior to treatment, MTV

was an independent predictor of OS. High MTV was also associated with an increased risk of locoregional failure at baseline and six months. In conclusion, pretreatment MTV was a strong predictor of clinical outcomes in lung patients receiving CRT.

Table 2.5 Studies that explored the role of PET integration to target delineation

study	Year, type	patients #	Stage	Volume changes due to FDG-PET
Nestle (82)	1999, Retrospective	34	IIIB-IV	-Field size reduction 26% -Change in size and shape of radiation fields: 35%
Bradley(81)	2004, prospective	26	IA (6) II (2) IIIA (13) IIIB (4) IV (1)	PTValternation:58% GTVreduction:12% GTV increase46%
van Der Wel A(83)	2005, prospective Simulated treatment	21	N2-N3M0	Nodal GTV decreased 3.8cm3 Dose to Lung and esophagus decrease
Ceresoli GL(84)	2007, prospective	21	This study explored the role of ENI	ENI with PET did increase the GTV but did not lead to unacceptable increase in RT toxicity
Faria SL(85)	2008, Prospective	32	III	GTV altered in 56% Decrease 37.3% Increase 18.7%
Yin LJ(86)	2013	30	III	All patients had Atelectasis in lung GTV alternation in 100% GTV decreased73.3% GTV increased 26.7%

2.3.4 Targeting RT better with FDG-PET: Volume delineation

For patients being treated with definitive RT, PET can aid with target delineation (90).

with the integration of PET into treatment planning at the primary tumor level, PET integration can lead to a decrease in GTV size by omitting the atelectic lung at GTV level. At the nodal level, it can affect nodal volume by further highlighting involved areas. The effect of PET

integration with tumor delineation has been studied in multiple studies(81-86). **Table 2.4** shows some of these studies along with the volume changes associated with PET integration. Studies have explored if these changes led to improvement in patients' outcomes.

2.3.5 Adaptive, FDG-avid, volume delineation and dose intensification.

Efforts for dose escalation were pursued by using adaptive radiotherapy and individualized RT. Individualized RT was compared with standard RT in a few studies(91, 92). Essentially, patients were randomized to individualized groups underwent CT and PET-based treatment planning at baseline and had CT re-simulation and PET-CT in the original position after delivering 18-20 fractions to tumor. Then, the outcomes between standard radiation and individualized treatment were compared. The Chinese RTOG (92) trial showed that the Overall survival Progression-free survival was significantly better in patients who received individualized dose-escalated treatment. RTOG1106(91) evaluated adaptive dose escalation radiotherapy in stage 3 lung cancer patients. The initial results were released recently, which did not show any significant difference between PET adaptive dose escalated group and the standard RT group(91)

2.4 Studies to Improve cCRT outcomes with Targeted Therapies

2.4.1 Targeted therapy in Stage III NSCLC

Various types of research identified several molecular pathways responsible for oncogenesis, cancer cell progression, growth and cancer resistance to radiation or other agents. Therefore, these pathways are being explored as potential targets to intensify RT or chemotherapy response. The

result has been an explosion of new molecularly targeted agents with potential value for selected lung cancer patients. Indeed, some of these agents have also been tested to be used as primary therapy for lung cancer patients with matching molecular profiles.

The expanding list of molecular targets for NSCLC includes epidermal growth factor (EGF)and its receptor (EGFR), vascular endothelial growth factor (VEGF) and its receptor (VEGFR), Anaplastic Lymphoma Kinase (ALK) fusion protein (EML4-ALK), B Raf, PIK3CAgene, ErbB2 (Her2/neu), mammalian target of rapamycin (mTOR), and various other molecules that regulate different steps in their signal transduction pathways. The most clinically advanced agents target EGFR, VEGF/VEGFR, and ALK1 pathways. Table 2.6 lists some trials that tried to target these pathways (93-97).

Table 2.6 Targeted therapy treatments in stage III NSCLC

Ref	Trial	Agent	Study Design	Result
(93)	RTOG 0324, phase 2	Cetuximab	Carboplatin/paclitaxel/cetuximab/RT→carboplatin/paclitaxel x 2 cycles	Median OS :27.7 Mo 2yOS: 49.3%
(95)	CALGB 30407, phase 2	Cetuximab	Carboplatin/pemetrexed/RT ± cetuximab	With Cetuximab 18 months survival 52% Without 58%
(96)	SWOG 0023, phase 3	Gefitinib	Chemo/RT ->docetaxel x 3 cycles → gefitinib *v* placebo	With placebo 35 With Gefitinib 23
(97)	CALGB 30106, phase 2	Gefitinib	Good-risk group: carboplatin/paclitaxel →RT/gefitinib/carboplatin/paclitaxel →gefitinib poor-risk group: carboplatin/paclitaxel →RT/gefitinib →gefitinib	Good-risk group: PFS 9.2 mo, median OS 13 months Poor-risk group: PFS 13.4 mo, median OS 19 mo
(94)	University of Chicago, phase 1	Erlotinib	Group 1: carboplatin/paclitaxel →carboplatin/paclitaxel/RT/erlotinib Group 2: cisplatin/etoposide/RT/erlotinib →docetaxel	Group 1: median OS 13.7 mo Group 2: median OS 10.2 mo

None of the trials on NSCLC patients showed benefit with these targeted agents.

2.4.2 Definitive Phase III trial of EGFR targeting in combination with cCRT in LA-NSCLC

The RTOG 0617 (76) evaluated the addition of cetuximab. The addition of cetuximab to carboplatin plus paclitaxel did not significantly improve OS (median, 25 versus 24 months; HR 1.07, 95% CI 0.84-1.35) and was associated with a significant increase in grade 3 or greater toxicity (86 versus 70 percent) in Cetuximab group.

2.4.3 Immune Checkpoint Inhibitors (ICIs)

Anti-PD-L1 trials and Immunotherapy

Efforts to improve outcomes of LA-NSCLC after chemoradiation by adding chemotherapy, targeted therapy or a combination of these were unsuccessful. Antonia et al. (98) have tried adding anti-programmed death ligand 1 antibody durvalumab as consolidation therapy in patients with stage III NSCLC. This was the first PACIFIC trial which assigned 709 stage 3 NSCLC patients in a 2:1 ratio to receive durvalumab (at a dose of 10 mg per kilogram of body weight intravenously) or placebo every 2 weeks for up to 12 months. The durvalumab treatment started 1 to 42 days after chemoradiation. Progression free survival and overall survival were the primary endpoints. The progression-free survival was 15.6 months in the treatment arm versus 5.6 months in the placebo arm. The response rate was 28.4% versus 16%, and the median time to death or distant metastasis was 23.2 months versus 14.6 months in the treatment arm versus the placebo arm.

In an update to the PACIFIC trial published in 2018 (99), the 2 years overall survival was 66.3% versus 55.6%, favouring durvalumab group. An update on progression-free survival showed a median duration of 17.6 months versus 5.6 months. The most recent update of the PACIFIC trial

was reported in ESMO 2020 and showed that the median Overall Survival for the durvalumab arm was determined for the first time: 47.5 months (placebo, 29.1 months). The 48-month OS rates were 49.6% vs 36.3% for durvalumab vs placebo, and PFS rates were 35.3% vs 19.5%, respectively. Newer trials are testing the effects of durvalumab plus cCRT versus cCRT alone in the PACIFIC 2 trial currently accepting patients.

2.4.4 Metabolic Targeting in combination with cCRT

Efforts to improve the patient's outcomes were continued by targeting metabolic pathways. In selected cancers, retrospective studies showed improved survival outcomes in diabetic patients treated with metformin during cancer treatment. Using these results as well as pre-clinical evidence indicating improved anti-tumor activity when metformin was added to RT, investigators examined the benefit of addition of metformin to SOC in LA-NSCLC. Metformin was investigated in combination with cCRT in stage III NSCLC in the phase 2 NRG-LU001 trial(100), which failed to show a clear benefit with the addition of metformin. The role of metformin was also evaluated in the ALMERA trial, which was also unsuccessful in showing benefit with the addition of Metformin to SOC cCRT(101).

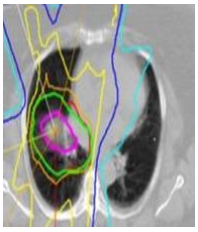
2.5 Trends in survival outcomes over time

The current standard of care for patients with LA-NSCLC is cCRT. While the improved imaging techniques and RT technologic improvement have improved outcomes in patients with early-stage

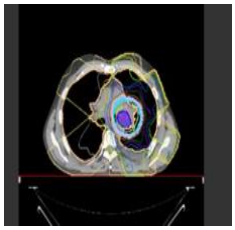
lung cancer, there has been little change in dose and fractionation in patients with LA-NSCLC. Nonetheless, survival for patients with LA-NSCLC has improved over time. Table 2.7 shows the improvement of survival with chemoradiation with time and correlated improvement with radiotherapy advancements.

Table 2.7 Survival Improvement during recent years in chemoradiation patients along with its correlation with technological advancements in radiotherapy

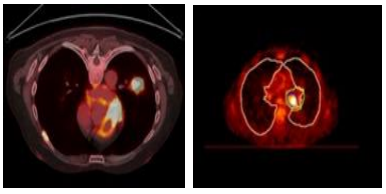
	NPC95-01	LAMP	CTRT99/97	CALGB 30105	CALGB 39801	HOGRTOG 0117	RTOG 0117	CALGB3 0407	RTOG 0324	RTOG 0617	PROCLAIM	PACIFIC
Median survival	16.3	16.3	18.7	24.3	14.0	23.2	21.6	21.2	22.7	28.7	26.8	28.7
Year	2005	2005	2006	2008	2009	2009	2010	2011	2012	2016	2016	2018



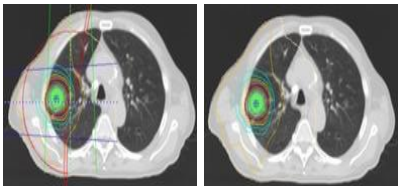
IMRT[1]



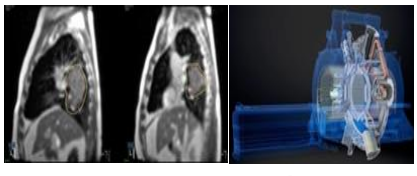
VMAT[2]



PET CT[3]



SBRT[4]



MRI Guided RT[5]

One reason for the improved survival of these patients is better staging before treatment with positron emission tomography CT (PET-CT) and endobronchial ultrasound transbronchial needle aspiration (80). PET-CT has been demonstrated to upstage 24% of LA-NSCLC cases to Stage 4 (102). Table 2.8 shows the improvement in survival which correlates well with technical advancements in the field of radiation oncology. Before 1980s, RT for lung cancer was planned in a simulator using parallel opposed fields and anatomical landmarks to define the target. The introduction of three-dimensional (3D) conformal RT using CT planning in the 1990s improved tumor coverage and reduced radiation dose to organs at risk (OARs). Additionally, conformal treatment has become possible with the advent of intensity-modulated radiotherapy (IMRT), in which the RT beam fluence, weight and shape are varied for multiple beams during treatment. Imaging capabilities have progressed alongside radiotherapy. Four-dimensional CT (4DCT), in which the respiratory motion of the tumor is taken into consideration, has facilitated even smaller margins synchronized to the patient's breathing cycle.

This motion adaptation will reduce the risk of a geographical miss in lung cancer RT (103). Cone beam CT (CBCT) has replaced two-dimensional megavoltage portal imaging to provide a more accurate set-up. Table 2.7 and the below figure shows the temporal association of radiation improvements with patient outcomes.

2.5.1 Radiotherapy alone outcomes

The vast amount of helpful literature on RT outcomes comes from when patients with good performance status were randomized to RT Versus CRT. This goes back to almost two decades ago. After the establishment of CRT as the standard of care for the treatment of LA-NSCLC, RT alone as a treatment lost its appeal among the researchers. As mentioned above, patient outcomes

in the CRT arm improved dramatically in the last 2 decades; there is an ongoing debate on how much of this improvement is related to radiation.

Evidence of RT alone outcomes during the last two decades comes mainly from population-based retrospective studies that often report radiation outcomes in a specific subgroup of patients that were unsuitable for the standard of care treatment. In the study by Franceschini et al. hypo-fractionated RT's role was explored in elderly patients with stage 3 lung cancer(104) Outcomes of hypo-fractionated RT were reported in the group of patients with a mean age of 78.6 years old, while median OS was 13.7 months, and OS at 12 and 18 months was 51.3% and 35.1%, respectively. Another retrospective study by Joo et al. reported patient outcomes in stage 2 and 3 lung cancer of patients over 60 years (105)[95] They reported median overall survival of 18.6 Months, while 2-year and 3-year overall survival were 39% and 23%, respectively. Wang et al. (106) reported 237 stage 3 lung cancer cases who received RT alone, cCRT and sCRT. In this study, for patients treated with RT alone, sCRT, and cCRT shows these retrospective studies.

There are well known weaknesses associated with retrospective studies, including: first, a great deal of data is missing, and because of that, specific statistics cannot be measured; progression-free survival (PFS) is one of these parameters. The second issue is the problem of selection bias. This bias can result from heterogeneity associated with stage 3 lung cancer patients. The studied specific patient subgroup may not represent the whole group. The third problem is that because of the nature of these studies, other factors associated with outcomes cannot be controlled. For example, when we are performing a retrospective study on outcomes of RT alone in stage 3 lung cancer patients, we may inadvertently include patients with low baseline performance, or patients with severe comorbidities. Ultimately these patients' outcomes could be low irrespective of the treatment they receive.

Other more popular studies are population-based studies that usually evaluate a large number of patients. These studies can provide some perspective on the proportion of patients receiving a specific treatment; Guo et al. (107) reported survival of patients in stage 3 in two different age groups, 65-74 and more than 75. In the former age group, it was shown that RT survival was 6 months, chemotherapy alone survival was 11 months, and survival with BSC (best supportive care) was around 3 months. The effectiveness of radiotherapy was evaluated in another population-based study; Keith Sigel et al. (108) reported an improvement in overall survival when radiotherapy was added to the treatment.

Of note, another study by Locolano et al. (109) compared hypofractionation radiotherapy with conventional radiotherapy in stage 3 lung cancer patients treated without chemotherapy. In this study median Conventionally Fractionated Radiotherapy (CFRT) dose was 66 Gy in 2 Gy fractions vs. 58.5 Gy in 2.5 Gy fractions for Hypo-fractionated Radiotherapy (HFRT). HFRT was associated with older age, lower biological effective dose (BED10), academic facility type, higher T-stage and lower N-stage. On initial analysis, HFRT was associated with inferior OS (median 9.9 vs. 11.1 months, $p<.001$), but after adjusting for the imbalance in covariates such as age, BED10, T-stage and N-stage using FDG-PET, the difference in survival was no longer significant ($p=0.1$). One of the prominent retrospective population-based studies was done in Ontario (110), which included patients with NSCLC from 2010 to 2015. There were 5243 patients with stage 3 lung cancer, more than 85% of these patients were unresectable. Concurrent chemoradiation was used in 22.1% of patients, palliative radiotherapy in 21.0%; curative radiotherapy was used in 19.6%; no treatment was used in 19.6%; chemotherapy alone was used in 11.6%; sequential chemoradiation in 5.4%, and targeted therapy in 0.7%. Median overall survival was 14.2 months; the poorest median overall survival was in those receiving no cancer treatment (5.9 months); The

median overall survival in patients receiving cCRT was 23.6 months. Curative RT survival was at 17 months, chemotherapy alone at 16.5 months, sequential chemotherapy at 14.4 months, and palliative radiotherapy at 7.1 months.

Population-based studies are not without flaws; first, most of these studies include old data; for instance, patients from 2010 were reported in a recent report published in 2020. Second, the RT techniques used in these studies were old fashioned. If we look at the development of radiation delivery during the last two decades, we realize that although we are delivering the same RT dose, the radiation delivery technique has changed dramatically. The third problem is the inconsistency in the use of PET in staging; in most of these studies, either PET was not used, or it was used on a portion of patients, making interpretation of results hard. Finally, database reliability is another major issue. In one of the studies, the methods that were used to classify radiation dose were deemed unreliable.

Table 2.8Radiotherapy alone studies in NSCLC

Ref	**Author and Year**	**Patients #**	**Patients' population**	**Outcomes**				
(107)	Guo	33530	2004-2014	Age	cCRT	RT	Chemo	BSC
				65-74	15	6	11	3
				>75	13	7	9	2
(108)	Sigel	10376	1992-2007	RT				
				9				
(109)	Locolano	6490	2004-2014	Hypofractionation		Conventional Fractionation		
				9.9		11.1		
(111)	Miller	23229	2003-2014	CRT		RT		
				17.2		12.2		
(106)	Wang	237	1992-2004		RT	sCRT	cCRT	
				Median Survival	7.4	14.9	15.8	
				5 Y OS	19.4%	7.5%	3.3%	

2.6 Conclusions

Although RT is the mainstay in the standard-of-care treatment of unresected LA-NSCLC, the contribution of modern RT to survival outcomes of standard therapy in well-staged patients with the disease is not well understood.

2.7 Hypothesis, Objectives and Aims

Hypotheses

Modern RT provides significantly improved survival outcomes in LA-NSCLC who are well staged. Use of definitive RT dose, staging FDG-PET and RT planning that spares heart tissue may improve survival outcomes in patients with unresectable LA-NSCLC.

Objectives

Main Primary objective:

Estimate contemporary survival outcomes of RT in well-staged patients with LA-NSCLC treated in a North American setting.

Main Secondary Objectives:

1. Estimate the impact of RT dose and modern staging with FDG-PET on overall survival.
2. Pursue an analysis of tumor and RT dosimetric parameters that may influence survival outcomes in this population.

Aims

Evaluation of RT outcome of patients with LA-NSCLC using retrospective analyses of:

1. Ontario provincial population data and
2. Regional institutional data from the Juravinski and Walkers Family Cancer Centers.

2.8 Methodology

2.8.1 AIM 1: Analysis of Provincial data

This first aim was a population-based analysis evaluating patients with stage III NSCLC treated with RT between January 2007 and March 2017.

The cohort was identified using the Institute of Clinical Evaluative Sciences (IC/ES) database.

IC/ES is a provincial database that contains health administrative data from multiple sources on all residents in the province of Ontario who receive universal health care. Most Ontario residents are insured through the Ontario health insurance plan; they are captured in IC/ES data through the public health care system.

2.8.2 AIM 2: Analysis of institutional data

To achieve that goal, chart review was done on all the patients with stage III lung cancer treated at Juravinski Cancer Centre and Walker Family Cancer Centre during 2009-2019.

The regional data analysis yielded a small number of well-staged patients that received high-dose curative RT for the treatment of stage III NSCLC. Having the clinical details and actual RT plans in our institutional databases permitted us to pursue a detailed analysis of the association of the outcomes of these patients with tumor characteristics and RT dosimetric details.

Specifically, we evaluated the association of survival outcomes with the following:

- RT clinical and planned tumor volume (CTV / PTV)
- Normal tissue RT doses, such as heart and normal lung.

Chapter III

Contemporary Real-world Radiotherapy Outcomes of Unresected Locally Advanced Non-Small Cell Lung Cancer (LA-NSCLC)

3.1 Abstract

Background: Radiotherapy (RT) is used as monotherapy in poor performance patients with unresected LA-NSCLC, but their outcomes are not well-described. As novel therapies are increasingly considered in this space, it is important to understand the contemporary outcomes of RT alone. Here, in this retrospective cohort study, we analyzed LA-NSCLC outcomes of RT alone in Ontario, Canada, and contrasted them against those of standard of care (SoC) treatment of concurrent chemo-radiotherapy (cCRT).

Methods: Ontario provincial databases were searched through the Institute of Clinical Evaluative Sciences (IC/ES) for stage III NSCLC patients diagnosed between 2007 and 2017. Surgical patients were excluded, and all patients that received RT with or without chemotherapy were selected. Patients were divided into groups of RT dose received (<40Gy, 40-55.9Gy, and ≥56Gy) and whether they underwent diagnostic ^{18}F-deoxy-glucose (FDG)-positron emission tomography (PET).

Results: 5,577 stage III patients that received chest RT without surgery between January 2007 and March 2017 were included in this analysis. Within this group, 39.8% (2,225) received RT alone, 47.4% (2,645) received concurrent chemoradiotherapy (cCRT), and 12.6% (707) received sequential chemoradiotherapy (sCRT). Median OS with RT alone in three dose groups <40Gy, 40-55.9Gy and ≥56Gy was 7.2, 8.5 and 13.3 months, respectively, compared to 16.5, 15.8 and 22 months for cCRT patients, respectively. Higher RT dose and PET utilization were independently associated with improved survival in multivariate analysis.

Conclusions: Radiation monotherapy remains a widely used treatment modality in LA-NSCLC. RT dose and utilization of FDG-PET imaging are associated with improved survival in this group. These findings help improve clinical decision making and serve as a basis for future trials.

3.2 Introduction

Lung cancer is a leading cause of cancer death worldwide (110). Non-small cell lung cancer (NSCLC) accounts for about 85% of newly diagnosed lung cancer (112). Approximately one third of NSCLC patients present with locally advanced (LA) NSCLC (corresponding to AJCC 8th ed. stage III), and most are not amenable to surgical resection (113). Until the 1990s, the standard of care (SoC) for unresectable NSCLC was radiotherapy (RT) alone. At that time, studies reported median OS and 5-year overall survival (OS) rates of 10 months and 7%, respectively (54). Successive trials in the past 30 years initially introduced sequential chemo-radiation (sCRT), and subsequently, concurrent chemo-radiotherapy (cCRT) without or with consolidation chemotherapy as SoC in stage III eligible patients. In RTOG-9410 cCRT improved median and 5-year OS to 17 months and 16%, respectively, compared to 14.6 months and 10%, with sCRT (61). In recent years, the addition of anti-Programmed Death Ligand 1 (PD-L1) immunotherapy (Durvalumab) as consolidation treatment after cCRT was shown to improve further median OS in unresectable LA-NSCLC further (47.5 months Vs 27.1 months) (114). Currently, cCRT in combination with consolidation anti-PD-L1 therapy are considered SoC. However, not all patients are able to receive this lengthy treatment. Examples include those with contraindications for chemotherapy, which precludes them from receiving Durvalumab also.

In recent years, population studies (110, 115-117) suggested that 39-52% of LA-NSCLC patients may be treated with RT alone (110, 116, 117). Although the contribution of modern RT techniques

to cCRT outcomes has been explored (118), there is a need to understand better the impact of modern RT when used as monotherapy. A study from Ontario, Canada, suggested that in the period of 2010-2015 only 22.1% of patients with stage III LA-NSCLC received cCRT, while 41% of patients received RT alone (110).

The above data indicate the clinical importance of understanding well contemporary real-world outcomes of RT alone. This is of increased value since outcomes of cCRT in unresected LA-NSCLC improve over time while the dose of chest RT and chemotherapy agents used in cCRT have not changed substantially. In 2011 Curran et al. (RTOG 9410 (61)) reported a median OS of 17 months for cCRT, but this increased to about 29 months in 2020 in RTOG-0617 (75). Similarly, RT alone yielded median OS of 10 months in historical trials (e.g., CALGB 8433, (1990) (57)), yet more recent, real-world data suggests the median OS can be as high as 17 months (110, 115). The etiology of these apparent improvements is unclear. Utilization of FDG-PET for staging and improvements in RT delivery techniques are suggested as potential reasons (119) (120). Although studies observe trends for improved survival outcomes, their association with the dose of chest RT or use of FDG-PET is not frequently examined.

Here, we pursued a population-based analysis of clinical treatment utilization data in the province of Ontario to obtain a contemporary view of the management of unresectable LA-NSCLC. We aimed to explore real-world outcomes of modern RT in stage III NSCLC patients and explore the association of RT dose and utilization of FDG-PET with patient survival outcomes. We focused on the outcomes of RT as monotherapy and contrasted them to those of patients receiving SoC cCRT.

3.3 Methodology

3.3.1 Patient Population

A population-based retrospective search of Ontario health information data was conducted through the Institute of Clinical Evaluative Sciences (IC/ES) to identify patients with stage III NSCLC (AJCC 8th-edition) that received chest RT from 2007 to 2017. Most Ontario residents are insured through the Ontario Health Insurance Plan (OHIP), and health administrative data on the services these residents receive can be accessed through IC/ES. Provincial databases were searched using the International Classification of Disease for Oncology morphology codes. Patients with stage III NSCLC receiving at least one RT dose within 180 days following diagnosis, with or without chemotherapy, were included. The choice of 180 days was selected as most patients would be expected to receive curative treatment within six months of diagnosis. This approach would exclude patients that received consolidation or palliative RT at later stages. Exclusion criteria included histology other than NSCLC, stage other than III, prior cancer less than 5 years from the NSCLC diagnosis, RT or chemotherapy prior to diagnosis, multiple cancers on the same day, and cancer surgery within 90 days of diagnosis. To distinguish between treatment regimen types and reduce survivorship bias, patients were included only if they had a follow-up of 60 days or more after the initial RT dose. Curative regimens of RT are typically six weeks (42 days) in duration, and the use of 60 days cut off ensured that most patients could have completed RT, including a possible delay, and then started chemotherapy, as per standard of care, if that was the regimen prescribed.

3.3.2 Analyses and Patient Categories

Patients were categorized into one of three treatment modalities: RT alone, cCRT or sCRT. A patient was defined to have received cCRT if at least one chemotherapy dose was administered between the first and last RT fraction, or at least one RT fraction occurred between the first and last dose of chemotherapy, within 180 days of RT. A patient was defined as having sCRT if they received chemotherapy within 180 days of RT but did not receive cCRT by definition above. A patient was defined as receiving RT only if they did not receive any chemotherapy within 180 days of RT.

Patients were divided into three RT dose categories of <40Gy, 40-55.9Gy and ≥56Gy. With an a/b ratio of 10 for lung cancer, these categories include RT schemas with BED <50Gy, 50-65Gy and >65Gy and encompass well schemas typically given for palliation, short-term local control or definitive treatment, respectively (**Table 3.s1**). Finally, patients were separated into groups that did or did not undergo staging FDG-PET.

Since income, distance from a cancer care facility and performance status can influence treatment selection and overall outcomes, we also included in our analysis models of income quintile, rurality, distance from a regional cancer center (RCC) and reported Charlson's score.

3.3.3 Statistical details

Descriptive statistics were used to summarize the patient population and outcomes. This study's primary outcome of interest was overall survival (OS), defined from the date of first treatment with RT to the date of death. The Kaplan-Meier method was used to estimate the OS outcomes, and patients not known to be deceased were censored on the last date they had contact with the

provincial health care system prior to 31 March 2019. Univariable Cox proportional hazards regression was used exploring the effect of selected prognostic factors on OS. An *a priori* selected subgroup analysis was performed to explore the effect of PET utilization within each RT dose group. A multivariable model was constructed based on the full model, i.e., including all factors explored in the univariable model. The only factor not included was the distance to the nearest cancer Centre, which was confounded with rurality. Interactions were explored between PET utilization, radiotherapy dose and treatment modality. Confidence intervals [CI] were constructed for outcomes of interest. All tests and CI were two-sided and statistical significance was defined at the α=0.05 level.

3.4 Results

3.4.1 Patient Characteristics and Utilization Patterns

Between January 2007 to March 2017, 110,690 individuals were diagnosed with lung cancer in Ontario. After excluding patients with non-NSCLC histology, stage other than III, those with multiple cancers on the same day, and patients with prior cancer, 14802 patients were found to have stage III NSCLC. After applying the remaining exclusion criteria, summarized in **Figure 3.1,** 5577 individuals were identified and included in this analysis. The baseline characteristics of the patients analyzed are presented in **Table 3.1.** Slightly more than half of the population consisted of males (53.5%; n=2985). Due to privacy concerns, the ICES database does not permit the extraction of individual age information. However, the distribution of age groups (in 10-year groupings) was obtained, and just over half of patients (50.2.%; n=2801) were 70 years or older.

Figure 3.1 Flow Diagram of selection of patients with unresected Locally Advanced Non-Small Cell Lung Cancer (LA-NSCLC) treated in Ontario in the period of 2007-2017.

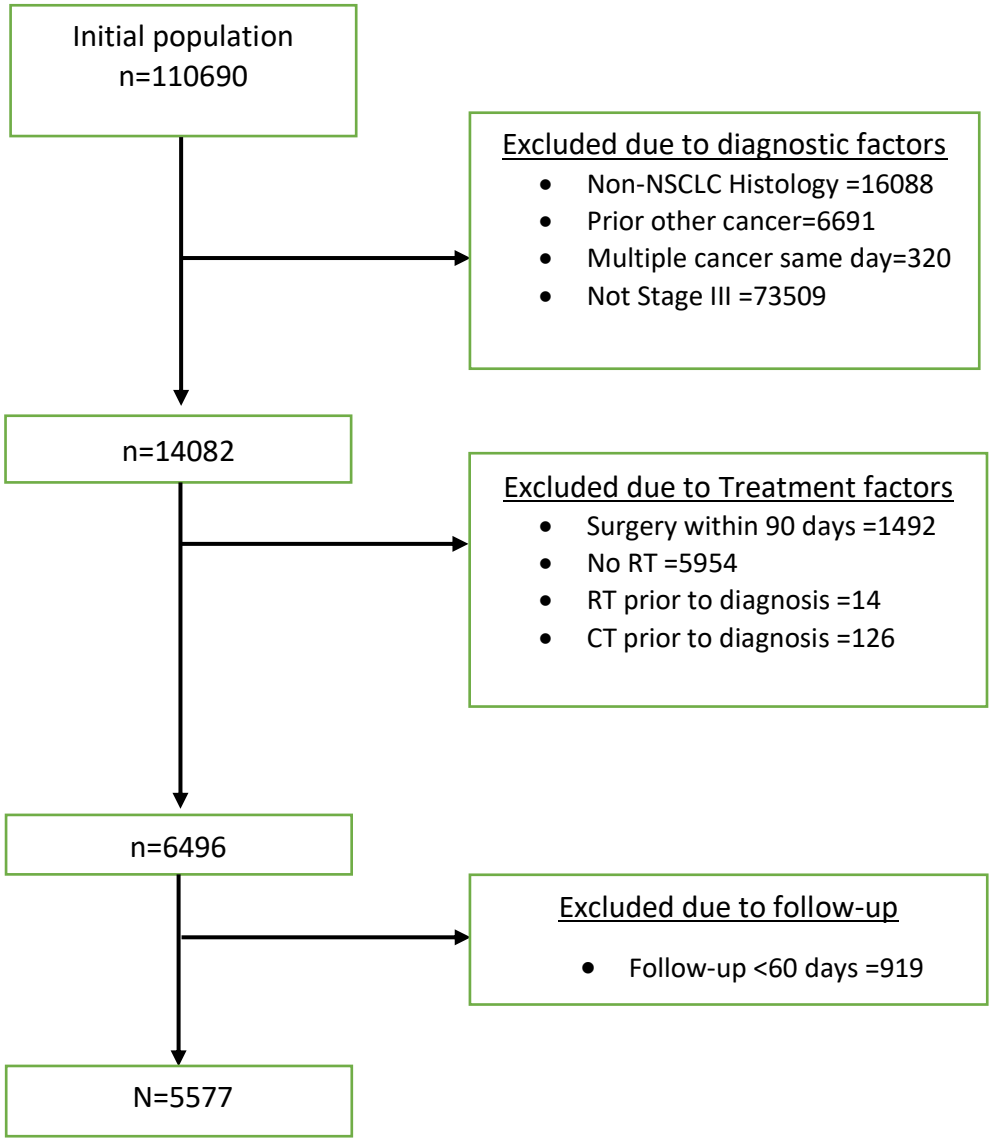
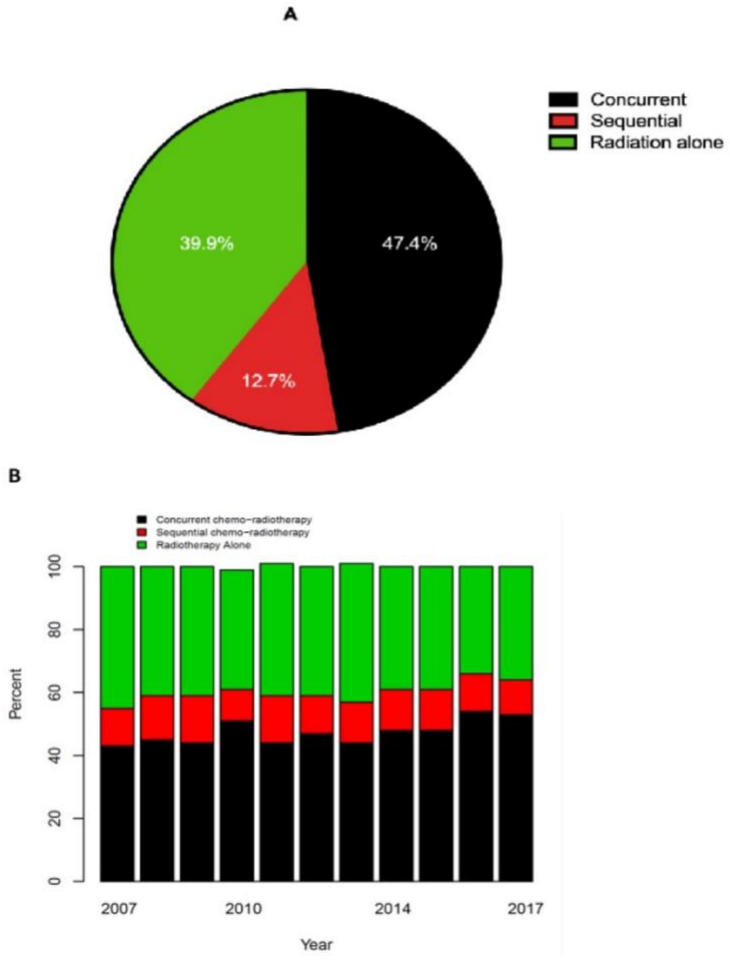


Table 3.1 Patient characteristics and outcomes

N	N		Statistic
Year of Diagnosis	5577	N (%) 2007-2010 2011-2014 2015-2017	2009 (36.0) 2071 (37.1) 1497 (26.8)
Sex	5577	N (%) Male	2985 (53.5)
Age Groups	5577	N (%) ≤59 60-69 70-79 80+	1083 (19.4) 1693 (30.4) 1901 (34.1) 900 (16.1)
Income Quintile	5565	N (%) 1 2 3 4 5	1386 (24.9) 1258 (22.6) 1061 (19.1) 1028 (18.5) 832 (15.0)
Rural Patient	5575	N (%) Yes	958 (17.2)
Distance to Nearest Cancer Centre, in KM	5573	Median (range)	17 (0, 653)
Known Charlson Score	5577	Median (range) N (%) ≥1	0 (0, 8) 677 (12.1)
Treatments within 180 days of Diagnosis			
PET Prior To RT Treatment	5577	N (%) Yes	2308 (41.4)
Radiotherapy	5577	Median (IQR) Days to Radiotherapy	55 (37, 82)
Radiotherapy Dose	5577	Median (IQR) <40 40 to 55.9 56+	34 (20, 60) 3015 (54.1) 586 (10.5) 1976 (35.4)
Chemotherapy modality	5577	Concurrent Sequential No Chemo	2645 (47.4) 707 (12.7) 2225 (39.9)
Chemotherapy	3352	N (%) Prior to RT	1176 (35.1)
Outcomes			
Overall Survival, from date of RT	5577	N (%) Deaths Median (95% CI) Months 1-year (95% CI) 2-year (95% CI) 5-year (95% CI)	4564 (81.8) 12.4 (11.9, 12.9) 51.1 (49.8, 52.5) 28.8 (27.6, 30.1) 12.2 (11.2, 13.2)
Overall Survival, Of Pts who received 40Gy+ Radiation	2562	N (%) Deaths Median (95% CI) Months 1-year (95% CI) 2-year (95% CI) 5-year (95% CI)	1979 (77.2) 17.8 (16.7, 18.7) 63.5 (61.5, 65.3) 39.1 (37.2, 41.1) 18.2 (16.6, 20.0)

RT was utilized as monotherapy in 2225 (39.8%) patients, while cCRT and sCRT were utilized in 2645 (47.4%) and 707 (12.6%) patients, respectively (**Fig 3.2 A)**. Thre use of cCRT appeared to increase slightly over time, but the use of sCRT remained relatively constant in this population (**Fig 3.2 B**). Within the group treated with RT alone, the majority of patients (1611, 72.4%) were treated with low-dose RT (<40Gy), while 292 (13.1%) and 322 (14.5%) received 40-55.9Gy and ≥56Gy, respectively. Conversely, within the cCRT group, 857 (32.4%) received <40Gy, 208 (7.9%) received 40-55.9Gy, and 1580 (59.7%) received ≥56Gy (**Table 3.s2**).

Figure 3.2 Utilization of radiotherapy without or with chemotherapy in patients with unresected locally advanced Non-Small Cell Lung Cancer (LA-NSCLC) in Ontario in the period of 2007-2017. A) Proportions of patients in each treatment modality for the entire period. B) Proportion of patients in each treatment modality each year.



Overall, 2308 (41.4%) patients had a PET scan prior to RT. There were 1315 (49.7%), 207 (29.3%) and 786 (35.3%) patients who had a PET scan amongst patients receiving cCRT, sCRT and RT alone, respectively. Alternatively, of all patients receiving <40Gy, 40-55.9Gy and ≥56Gy, 1057 (35.1%), 217 (37.0%) and 1034 (52.3%) underwent imaging with FDG-PET.

3.4.2 Outcomes

The median OS of the entire cohort was 12.4 months (95%CI: 11.9-12.9). Factors associated with survival are shown in **Table 3.2.** In univariate analysis, year of diagnosis, sex, age, income quartile, Charlson score, use of chemotherapy and increasing dose of RT were associated with improved survival. However, only gender, use of chemotherapy, higher RT dose and staging with FDG-PET maintained significance in multivariable analyses. Males (HR=1.18, 95% CI=1.12-1.25) and patients who received cCRT (HR=0.51, 95%CI=0.48-0.56) or sCRT (HR=0.80, 95%CI=0.72-0.88) had improved survival relative to patients who received RT alone. Increasing dose of RT was also associated with improved survival (HR=0.85, 95%CI=0.77-0.93 for 40-55.9Gy and HR=0.70, 95%CI=0.65-0.75 for ≥56 Gy versus patients who received <40Gy). Patients with baseline PET imaging also had significantly improved survival (HR=0.87, 95% CI=0.81-0.93). Survival estimates by chemotherapy modality, RT dose and PET utilization for patients in RT alone and cCRT groups are given in **Table 3.3** (for patients in sCRT group in **Table 3.s3**).

Figure 3.3 (A&B) illustrates Kaplan-Meier survival curves for patients in the RT alone and cCRT groups in the described RT-dose and PET utilization categories (**Figure 3.s1** reveals Kaplan-Meier survival curves for patients in sCRT group).

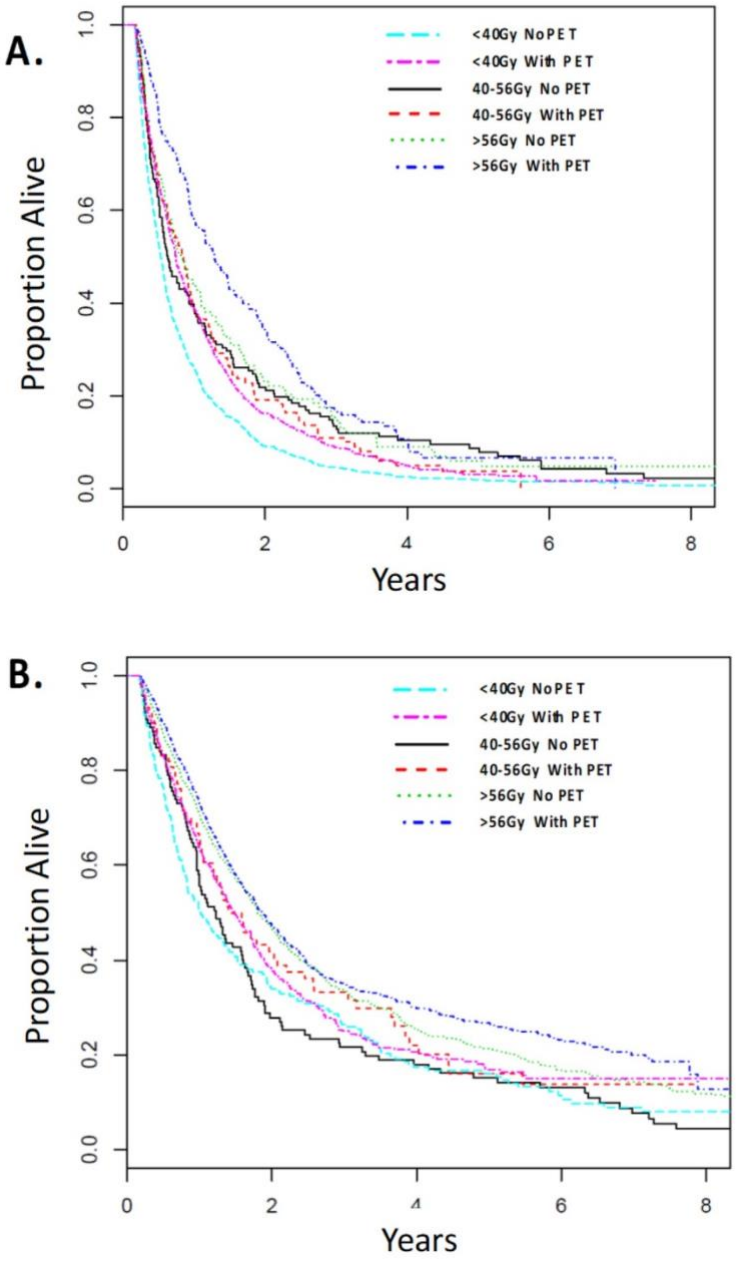
Table 3.2 Prognostic Factors of Overall Survival Beyond Landmark Time of 60 Days Following RT

		N	HR (95% CI)	p-value
Year of Diagnosis	/ Year	5577	0.99 (0.98, 1.00)	0.006
Sex	Male vs Female	5577	1.19 (1.12, 1.26)	<0.001
Age Groups	/ Group	5577	1.10 (1.08, 1.12)	<0.001
Income Quintile	/ Quintile	5565	0.97 (0.95, 0.99)	0.005
Rurality	Yes, vs No	5575	1.06 (0.98, 1.14)	0.17
RCC Distance	/ Km	5573	1.00 (1.00, 1.00)	0.76
Known Charlson Score	>=1 vs 0	5577	1.20 (1.10, 1.31)	<0.001
Chemotherapy	Yes, vs No	5577	0.49 (0.46, 0.52)	<0.001
PET Prior to RT	Yes, vs No	5577	0.77 (0.73, 0.82)	<0.001
Chemotherapy	Concurrent Sequential None	5577	0.43 (0.40, 0.46) 0.81 (0.74, 0.89) Reference	<0.001
Radiotherapy Dose	<40 40-55.9 56+	5577	Reference 0.84 (0.76, 0.92) 0.52 (0.49, 0.55)	<0.001
PET Prior to RT, by RT Dose	Yes, vs No for: <40 40-55.9 56+	 3015 586 1976	 0.78 (0.72, 0.85) 1.02 (0.85, 1.23) 0.88 (0.79, 0.97)	 <0.001 0.80 0.012
Multivariable Analysis				
Year of Diagnosis	/ Year	5565	0.99 (0.98, 1.00)	0.12
Sex	Male vs Female		1.18 (1.12, 1.25)	<0.001
Age Groups	/ Group		1.02 (1.00, 1.03)	0.097
Income Quintile	/ Quintile		0.99 (0.97, 1.01)	0.18
Rurality	Yes, vs No		1.05 (0.97, 1.14)	0.21
Known Charlson Score	>=1 vs 0		0.96 (0.88, 1.05)	0.40
Chemotherapy	Concurrent Sequential None		0.51 (0.48, 0.56) 0.80 (0.72, 0.88) Reference	<0.001
Radiotherapy Dose	<40 40-55.9 56+		Reference 0.85 (0.77, 0.93) 0.70 (0.65, 0.75)	<0.001
PET Prior to RT	Yes, vs No		0.87 (0.81, 0.93)	<0.001

Table 3.3 Overall survival by treatment modality, chest radiotherapy dose and PET utilization for patients with more than 60 days follow up.

	RT Dose (Gy)	PET	Median (95% CI)	1-year (95% CI)	2-year (95% CI)	5-year (95% CI)
Radiation alone	<40	**All (n=1611)**	**7.2 (6.9, 7.6)**	**31 (29, 34)**	**12 (10, 14)**	**2 (2, 3)**
		No PET (1109)	6.6 (6.2, 7.0)	28 (25, 30)	10 (8, 12)	2 (1, 3)
		PET (502)	8.8 (7.8, 9.7)	39 (35, 43)	16 (13, 19)	2 (1, 5)
	40-55.9	**All (n=292)**	**8.5 (7.3, 10.6)**	**39 (33, 45)**	**21 (16, 26)**	**7 (4, 10)**
		No PET (173)	7.5 (6.6, 9.7)	37 (30, 44)	21 (15, 28)	7 (4, 12)
		PET (119)	10.3 (7.6, 12.2)	42 (33, 51)	20 (13, 29)	6 (2, 12)
	56+	**All (n=322)**	**13.3 (11.2, 15.7)**	**53 (47, 58)**	**30 (25, 35)**	**7 (4, 10)**
		No PET (157)	10.8 (8.5, 13.8)	47 (38, 54)	26 (19, 34)	7 (3, 12)
		PET (165)	**15.4 (12.3, 19.2)**	**59 (51, 66)**	**34 (26, 41)**	**7 (3, 13)**
Concurrent-Chemo-radiotherapy	<40	**All (n=857)**	**16.5 (14.9, 18.4)**	**60 (57, 63)**	**37 (34, 41)**	**17 (14, 20)**
		No PET (451)	15.8 (13.6, 17.9)	58 (53, 62)	37 (32, 42)	17 (13, 22)
		PET (406)	**17.8 (15.2, 20.6)**	**63 (58, 68)**	**37 (32, 42)**	**17 (12, 22)**
	40-55.9	**All (n=208)**	**15.8 (12.6, 19.2)**	**61 (54, 67)**	**33 (27, 40)**	**16 (11, 22)**
		No PET (138)	15.4 (12.0, 19.1)	58 (50, 66)	31 (23, 39)	15 (9, 21)
		PET (70)	16.8 (12.2, 24.3)	65 (53, 75)	39 (27, 51)	19 (10, 31)
	56+	**All (n=1580)**	**22.0 (21.0, 23.8)**	**72 (70, 74)**	**47 (44, 50)**	**24 (22, 26)**
		No PET (741)	21.4 (19.5, 23.8)	71 (67, 74)	46 (43, 50)	21 (18, 24)
		PET (839)	**23.0 (21.1, 25.0)**	**74 (71, 77)**	**48 (44, 51)**	**28 (24, 31)**

Figure 3.3 Kaplan-Meier Curves of OS survival. A. Radiotherapy Alone. B. Concurrent Chemo-Radiotherapy



Interactions between PET utilization and chemotherapy modality and between RT dose and chemotherapy modality were both statistically significant. Thus, interpretation should be performed separately for each RT/cCRT/sCRT and dose group, not as an additive effect. Follow-up was a minimum of 1.25 years (end of 2017 was the last patient's diagnosis date, end of follow up was 31 March 2019)

3.5 Discussion

This analysis aimed to evaluate patterns of care and RT outcomes of unresected LA-NSCLC in Ontario, Canada, in recent years. The real-world survival outcomes of modern RT used as monotherapy is reported in this study. FDG-PET utilization was included in this analysis to help understand better the potential impact of RT dose in well-staged patients. We need to emphasize that, given the reasons for a patient to receive RT as monotherapy vs cCRT, performance status is an unmeasurable confounder, and the effect sizes observed cannot be assumed to be causal. Results in this report should therefore be used solely to improve our understanding of RT alone outcomes in a contemporary real-world North American setting.

Concordant with previous reports (110, 115-117), we found that a significant proportion of patients in our cohort from Ontario were treated with RT alone (39.8%) (**Fig 3.2A**). Trends of treatment use (RT alone vs cCRT or sCRT) have changed slightly over the years in favor of cCRT, but overall remained similar in the period 2007 – 2017 (**Fig 3.2B**). Notably, 27.6% of patients that received RT alone were treated with RT doses higher than those typically used for palliation (>40Gy), indicating that RT is perceived as a potentially useful tool for local disease control too.

Figure 3.3 illustrates i) the average performance of RT alone treatment in LA-NSCLC patients receiving contemporary chest RT in Ontario, ii) how OS relates to RT dose and FDG-PET utilization and iii) how these compare with outcomes of good performance status patients receiving SoC treatment.

The higher OS observed in the RT alone group managed with increased RT dose and PET utilization are indeed important. Although increasing RT dose did not translate to substantial absolute improvements in long-term (i.e., 5-year) OS in this group, median, 1-year and 2-year OS show significant improvements with the use of high-dose RT. We believe that short-term outcomes are more reliable evaluators of potential treatment benefits in patients receiving RT alone. The group of patients treated with RT alone is characterized by poor performance status and comorbidities, which determine long-term survival. Nevertheless, the higher dose of chest RT appears feasible and effective in selected patients.

In our cohort, patients that received curative dose RT as monotherapy (≥56Gy) had a median OS rate of 13.3 months, which increased to 15.4 months in PET-staged patients. While not formally comparable, these values are higher than historical clinical trials (such as CALGB 8433 (57) and RTOG 8808 (59); with median OS of 10 and 11 months, respectively). Discrepancies between values from historical trials versus modern studies may be due to various factors, including FDG-PET based staging, improved RT planning and RT delivery with Intensity-Modulated- (IMRT) and Image-Guided RT (IGRT) (110) (75, 119). There is limited contemporary randomized clinical trial data on OS achieved with curative dose RT alone. Recently, a phase III randomized trial that accrued in US centers between 2012 and 2018 reported RT-alone outcomes in patients treated with either conventional (60Gy in 30 fractions) or hypo-fractionated RT (60Gy in 15 fractions) (121). FDG-PET imaging was optional in that study. Hypo-fractionated RT did not offer overall benefit,

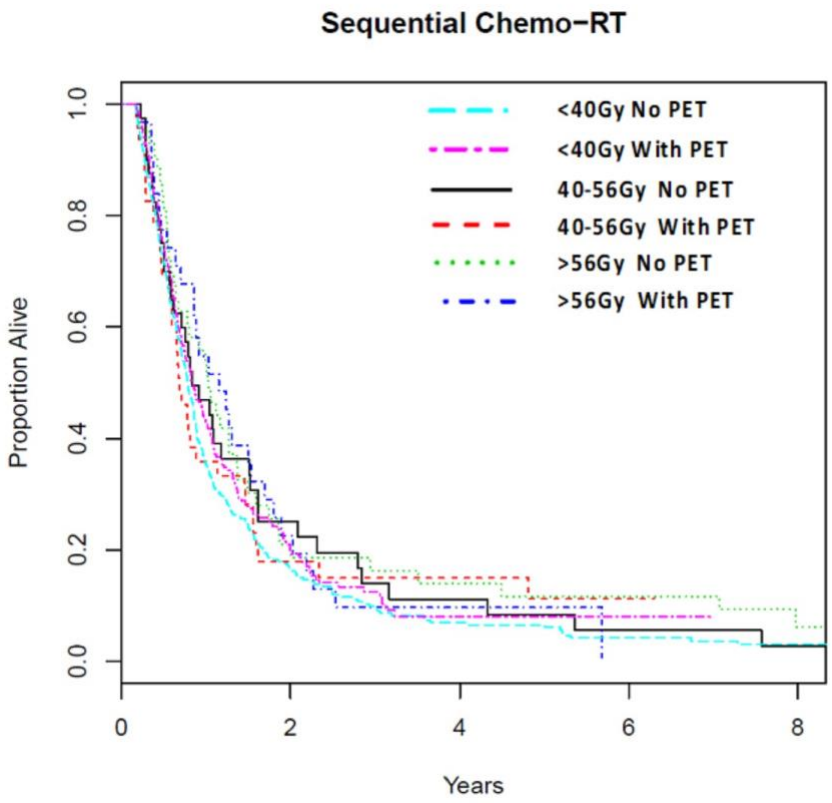
and conventional RT showed 1-year and 2-year OS of 44% and <30%, respectively. In comparison, 1-year and 2-year OS in our cohort with RT-alone of ≥56Gy were 53% and 30% for the entire group, increasing to 59% and 34%, respectively, for those staged with FDG-PET, indicating the value of ongoing investigation of RT-alone outcomes in LA-NSCLC.

In our cohort, the OS of patients treated with cCRT is lower compared to those reported in recent landmark trials of cCRT without or with consolidation immunotherapy, such as RTOG 0617 (75) and PACIFIC (114), respectively. These trials showed median and 2-year OS of 29 months and 55-57.65% for standard cCRT vs 21-23.0 months and 46-48% in this study. Further, very recently reported phase II randomized trials that accrued stage IIIA-B NSCLC patients (staged with FDG-PET) in the US and Canada in the past 7 years reported higher 2-year OS of 65-66% with standard cCRT alone (101, 122). SoC therapy outcomes may improve over time, which will likely be reflected in future reports of population outcomes.

In this study, FDG-PET utilization was associated with higher median OS, regardless of RT dose. The contribution of FDG-PET was not analyzed in prior population studies of RT-alone outcomes. However, other reports in LA-NSCLC suggested a positive correlation of PET utilization with improved OS. In a secondary analysis of the PROCLAIM trial (123), patients staged with FDG-PET showed trends for longer median OS vs those who were not (median OS 27.2 months vs 20.8 months; non-significant). While their data did not reach statistical significance for OS, median progression-free survival (mPFS) was significantly longer in the PET-staged group (11.3 vs 9.2 months). A frequently cited reason for the benefit of baseline FDG-PET is the effective exclusion of metastatic patients resulting in stage migration. However, PET may also contribute to improved outcomes by improving tumour delineation during RT planning (80, 81, 83-86, 120, 124), leading to improvements in tumor targeting and reduced toxicity through sparing of organs at risk.

This study did not aim to analyze the impact of chemotherapy on outcomes. Therefore, sCRT outcomes are not discussed in detail here (see **Table 3.s3** and **Figure 3.s1**). Expectantly, the use of sCRT is associated with improved OS compared to RT monotherapy but inferior compared to cCRT, in agreement with other studies (57, 61). However, the parameters set to select this group of patients aimed to be more inclusive of patients treated with both radiotherapy and chemotherapy, but not cCRT, and were not designed to select patients that are typically planned to receive sCRT.

Figure 3.S1 Kaplan-Meier Curves of OS survival. Sequential Chemo-Radiotherapy.



Other factors, such as access to cancer care due to income inequalities and distance from a cancer care facility, are often described to potentially influence outcomes in lung cancer patients in North America and worldwide (125). We found that such trends may exist in patients receiving care in Ontario centers; however, these factors did not predict OS independently. Future studies should investigate these factors more as they relate to specific treatment centers in Ontario or other jurisdictions.

Our study has several shortcomings. Population-based evidence is retrospective and limited by the detail and quality of data. While IC/ES provides reliable access to health service utilization in Ontario, the database does not include information on the intent of the RT treatment regimen, or the intent of staging investigation used. We attempted to reduce the effects of survivorship bias by selecting patients with an available follow-up of greater than 60 days. However, this type of "landmark analysis" does not completely eliminate all potential biases within the data. Lack of PET utilization in some patients may have been due to limited use of FDG-PET in the early years of its introduction into clinical practice as well as long wait times or patient specific factors. It should also be recognized that, apart from FDG-PET, more systematic use of brain magnetic resonance imaging (MRI) and mediastinal staging over the past 15 years have likely contributed to further improvement of outcomes in patients with LA-NSCLC through stage migration. Future population studies can analyze the impact of these factors. Finally, SoC in unresected LA-NSCLC is evolving rapidly. The data presented in this study illustrate outcomes of RT or CRT alone, as Health Canada did not approve consolidation anti-PD-L1 therapy (Durvalumab) until May 2018. Given the results of the PACIFIC trial (114), patients receiving SoC treatment today are expected to show improved OS rates that may be detected in future analyses.

3.6 Conclusions

This real-world data analysis from the province of Ontario illustrates that many patients with LA-NSCLC continues to be managed with RT alone. In this understudied population, we find that higher chest RT dose and utilization of staging FDG-PET are associated with improved OS. These results provide important information to support clinical practice and future prospective clinical trials in this group of patients.

3.7 Supplemental Data

Table 3.s1 Biological Effective Dose calculations (BED) of chest radiotherapy schemas used frequently.

BEDs of typical chest radiotherapy schemas				
			Alpha/beta ratio	
			10	
Total dose (GY)	**Number of fractions**	**Dose per fraction**	**BED**	**BED Groups**
20	5	4	**28**	**< 50**
30	10	3	**39**	
40	20	2	**48**	
40.2	15	2.68	**50.97**	**50-65**
45	15	3	**58.5**	
50	25	2	**60**	
54	27	2	**64.8**	
56	28	2	**67.2**	**>65**
60	30	2	**72**	
63	30	2.1	**76.23**	
60	20	3	**78**	
66	30	2.2	**80.52**	
60	15	4	**84**	

Table 3.s2 Patients analyzed by radiotherapy dose and treatment modality

Radiotherapy dose		N	RT <40 Gy	RT 40-55.9 Gy	RT ≥56 Gy
Chemotherapy modality	Concurrent Sequential None	2645 707 2225	857 (32.4) 547 (77.4) 1611 (72.4)	208 (7.9) 86 (12.2) 292 (13.1)	1580 (59.7) 74 (10.5) 322 (14.5)
Total		5577	3015 (54.1)	586 (10.5)	1976 (35.4)

Table 3.s3 Overall survival 60 days after radiotherapy for patients treated with sequential chemo-radiotherapy

Chemotherapy	**RT Dose**	**PET**	**Median (95% CI)**	**1-year (95% CI)**	**2-year (95% CI)**	**5-year (95% CI)**
Sequential Chemo-RT	<40	All (n=547)	9.8 (9.0, 10.3)	39 (34, 43)	18 (15, 21)	7 (5, 10)
		No PET (398)	9.3 (8.5, 10.3)	36 (31, 41)	18 (14, 22)	6 (4, 10)
		PET (149)	10.7 (9.3, 12.9)	46 (37, 54)	18 (12, 26)	10 (5, 17)
	40-55.9	All (n=86)	9.5 (7.8, 13.0)	41 (30, 52)	21 (13, 31)	9 (4, 17)
		No PET (58)	11.0 (8.6, 17.5)	48 (35, 61)	25 (15, 37)	11 (4, 21)
		PET (28)	7.2 (4.5, 8.3)	26 (11, 44)	13 (3, 29)	9 (2, 24)
	56+	All (n=74)	12.5 (10.3, 15.7)	54 (42, 65)	22 (13, 32)	10 (4, 19)
		No PET (44)	12.5 (7.8, 15.3)	55 (39, 68)	18 (9, 37)	11 (4, 23)
		PET (30)	13.8 (10.3, 21.6)	53 (34, 69)	27 (13, 43)	7 (1, 23)

Number of patients by dose and PET utilization are given. Median overall survival (mOS), as well as 1-year, 2-year and 5-year overall survival (1-yr OS, 2-yr OS, 5-yr OS) rates are given for each cohort, in aggregate as well as by dose grouping and utilization of PET imaging. mOS is given in months. Ranges in brackets are 95% confidence interval.

Chapter IV

Institutional survival outcomes and dosimetric data of stage III non-small cell lung cancer patients

4.2 Introduction

While population-based studies can be of great value in giving a general perspective on treatment type and patients outcomes, a more detailed analysis is warranted to explore other parameters associated with patients' survival. Tumor characteristics and dosimetric data are among the parameters that are not captured in most population-based studies. Investigation at an institutional level, where actual radiotherapy plans for each patient are available, permits analysis of specific dosimetric parameters and investigation whether such treatment characteristics influence survival.

Multiple dosimetric analyses have pointed out the importance of planning constraints in lung cancer patients. Studies have evaluated the role of Gross Tumor Volume (GTV) and its association with survival in patients with stage III disease. Koo et al.(126) found that smaller pretreatment GTV was associated with significantly improved survival and progression free survival of LA-NSCLC patients. Planning Tumor Volume (PTV) association with survival was studied by Karin et al.(127). This comprehensive single center study showed that PTV > 700cc was an independent prognostic factor of survival in LA-NSCLC patients.

On the other hand, unintentional treatment of normal chest tissues with radiation during chest radiotherapy for lung cancer has been a concern since the introduction of this treatment modality. Toxicity developing as a result of normal tissue irradiation is known to influence the patients' ability to receive curative treatment and affects negatively radiotherapy outcomes overall.

The rate of radiation pneumonitis was found to be correlated with overall survival of NSCLC patients and lung V20 was found to have correlation with progression free survival (128). Normal lung dose is lowered with modern radiation therapy techniques such as IMRT, which has

decreased the rate of radiation pneumonitis and permit a larger proportion of patients to receive curative dose RT (78, 128).

Esophageal radiation dose received during chest RT is an important predictor of esophagitis(129) which can to treatment interruptions. It is known that interruptions of radiotherapy decrease long-term survival of patients with unresectable non-small cell carcinoma of lung (130).

Further, as discussed in Chapter II (2.2.3), the cardiac dose has been suggested to be correlated with survival in different studies(79, 131). In a secondary analysis done on the landmark trial RTOG-0617(78), IMRT was associated with a lower dose to the heart, and heart dose was associated with the survival of LA-NSCLC patients. Cardiac dose association with survival was analyzed and modeled for this study(132).

To examine whether dosimetric parameters are indeed associated with survival outcomes in a real-world setting, outside clinical trials, we decided to pursue an analysis of dosimetric parameters in radiotherapy plans from patients treated in our Local Health Integration Network (LHIN4). LHIN4 includes the radiotherapy facilities of the Juravinski and the Walker Family Cancer Centers. Survival data of patients in our LHIN are submitted to the provincial databases and were, therefore, included in the provincial population-based analysis described in Chapter III. In this part of the thesis (Chapter IV), we first analyzed survival data of unresected stage III patients treated with RT alone or the SOC of cCRT to help identify similarities or differences between our specific regional population and those of the province of Ontario overall. Then we pursued a detailed analysis of radiotherapy plans of each patient to identify key dosimetric characteristics that may be able to predicts outcomes in LA-NSCLC patients managed with chest radiotherapy.

4.3 Methodology

4.3.1 Patients and Treatments

This study was approved by Hamilton Integrated Research Ethics Board (HiREB) with approval number 10652. A search was performed on the database of clinical management software MOSAIQ used in the two cancer care and radiotherapy facilities of LIHN4, the Juravinski and the Walker Family Cancer Centers. The search was set to identify patients who received chest radiotherapy from January 2009 to December 2019.

Patients with stage III LA-NSCLC (AJCC v7.0) were selected based on staging investigations that included chest X-ray, chest computed tomography (CT), bronchoscopy, FDG-PET, brain CT or magnetic resonance (MR), bone scan, mediastinoscopy or endobronchial ultrasound (EBUS.

Only patients who received a dose of chest RT of 40Gy or higher were included in this study. This dose limit was selected to exclude patients treated with palliative intent, as most RT schemes below 40Gy are given for palliation. Patients were grouped based on their treatment. Three groups of patients were identified: patients who received RT alone, cCRT and sCRT. Patients who received sCRT were excluded from this study.

The RT alone group received only radiation with no chemotherapy within 180 days after diagnosis. cCRT patients were those who received at least one dose of chemotherapy during the RT treatment.

4.3.2 Radiotherapy treatment.

RT was targeted to the primary tumor, and clinically involved nodes in all patients analyzed in this study. The lymph node was included and treated if it was more than 1cm in greatest diameter, had an increased standard uptake value in FDG-PET or was positive in the biopsy. Elective nodal irradiation was not used routinely in the treatment of our patients.

The radiation dose used in the concurrent chemoradiation group was 60-63 Gy in 30 fractions. CT simulation scan was used for planning.

4.3.3 Dosimetric analysis data

We pursued dosimetric analysis for patients in the RT alone and cCRT groups. The patients' RT plans were restored in our institutional planning system (Pinnacle, Philips, USA) by Juravinski Cancer Center physics staff (Dr.Tom Chow). Then a Python-based workflow script was written specifically for this study to read the dosimetric data file and export the results to an excel sheet by Dr. Orest Ostapiak. Then, dosimetric data of each person were exported to a file. Tumor Clinical Target Volume (CTV) and Planned Target Volume (PTV) as well as normal tissue, heart, esophagus and lung volume were reviewed, updated and RT doses into those volumes were calculated with the generation of standard planning dose–volume histograms (DVH). Dosimetric data of each person were exported to a file and all data were subjected to early statistical analysis.

4.3.4 Statistical Analysis

Descriptive statistics were used to summarize the patient population and outcomes. The primary outcome was overall survival (OS), defined from the date of diagnosis to the date of death. Kaplan-

Meier method was used to assess the OS outcomes, and patients not known to be deceased were censored on the last date they had contact with the Juravinski cancer centre.

Univariable Cox proportional hazards regression was used to explore the effect of selected prognostic factors on OS. A multivariable model was constructed based on forward stepwise selection, amongst all factors explored in the univariable model. Subgroup analyses were performed based on treatment received (chemotherapy and radiotherapy or radiotherapy alone). Confidence intervals [CI] were constructed for outcomes of interest. All tests and CI were two-sided and statistical significance was defined at the $\alpha=0.05$ level**.**

4.4 Results

4.4.1 Patients Characteristics and treatments

A total of 268 patients were identified in our institutional database that satisfied the above-described parameters. Of these patients, 184 were treated with concurrent chemoradiation (cCRT), and 84 were treated with RT alone. The mean age of patients who received RT alone was 76.4, and the mean age in cCRT was 66.0. 53.6% of patients in the RT group were male, whereas 51.1% in the cCRT group were male. The median day from diagnosis to radiotherapy was 29 (5-54) days in the RT alone group, whereas in the cCRT group was 44 (18-64) days, which could be related to more completed diagnostic evaluation in the cCRT group.

The distribution of pathologic type in the RT alone group revealed that 45.2% were adenocarcinoma, 51.2% were squamous cell carcinoma, and 3.6% were Carcinoma, NOS (Not otherwise specified). In the cCRT group, the distribution was almost similar, revealing 52.2%

adenocarcinoma, 44% squamous cell carcinoma, 2.2% carcinoma (NOS), 1.1 % large cell carcinoma, and 0.5% adenosquamous cell carcinoma.

This analysis is based on the patient's staging category reported in the chart (based on AJCC 8th version). In a small portion of these patients, the staging was not subclassified, but was reported to be stage III (9.5% of the cases in the RT group and 8.2% of cases in the cCRT group were reported to have stage III disease without subclassification to A or B or C). Stage subclasses (were similar in both groups; in the RT alone group, 63.1% were stage IIIA, whereas 63.6% in the cCRT group were stage IIIA. In the RT alone group, 26.2% were staged IIIB, almost similar to 28.3% in the cCRT group. Only 1.2 % (one case) in the RT group was stage IIIC, and none of the cCRT cases was stage IIIC.

One of the most striking differences between these two groups was the radiation dose and fractionation. In the cCRT group, patients received consistently higher doses than the RT alone. A 69.1% of patients in the RT alone group received less than 60 Gy, which is dramatically higher than the 15.8% of cases in the cCRT group that received a dose of less than 60 Gy.

Chemotherapy type distribution used in the cCRT patients was as Cisplatin/Etoposide combination in 82.1%, Carboplatin/Etoposide in 12, Cisplatin/Pemetrexed in 3.3%, Carboplatin/Paclitaxel in 1.6%, and finally, Cisplatin/vinorelbine in 1.1% of the cases. Another difference between these two groups was the proportion of patients staged with FDG-PET. A 79.8% of patients in the RT alone group were staged with PET, while a higher proportion of patients in the cCRT group (95.1%) were staged with PET. Patient's characteristics and outcomes are summarized in **Table 4.1**.

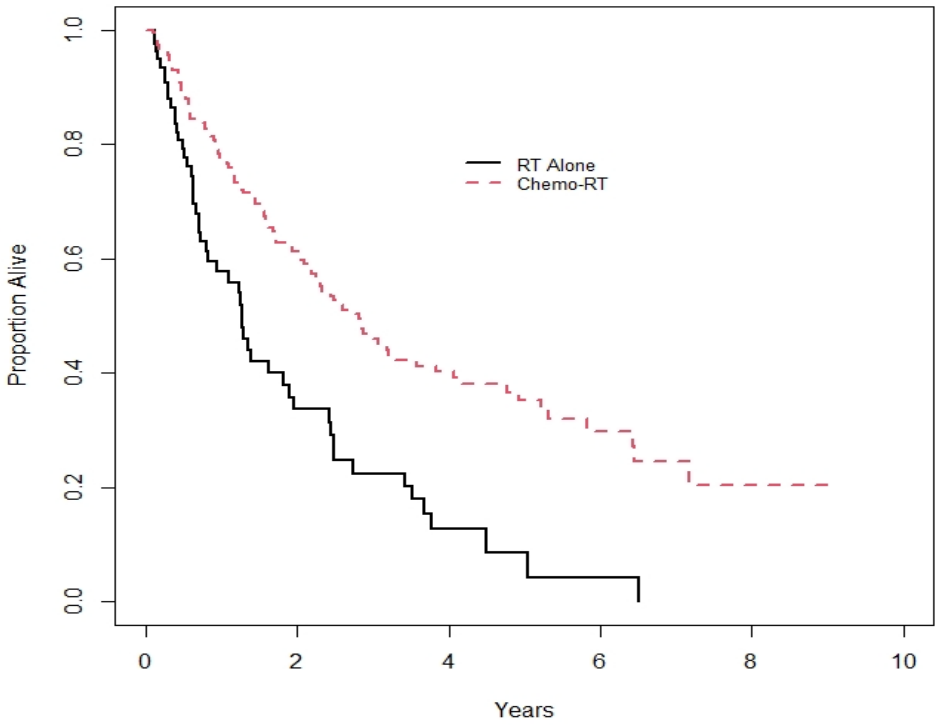
Table 4.1 patient's characteristics and outcomes

	Variable	N	RT Only	Chemo-Rad	p-value
N			**84**	**184**	
Age at Dx	Mean (sd)	268	76.4 (9.2)	66.0 (8.6)	<0.001
Sex	N (%) M	268	45 (53.6)	94 (51.1)	0.79
Dx to RT, days	Median (range)	268	29 (5, 54)	44 (18, 64)	<0.001
Morphology	Adenocarcinoma Adenosquamous Carcinoma, NOS Large Cell Carcinoma Squamous Cell Carcinoma	268	38 (45.2) 0 (0) 3 (3.6) 0 (0) 43 (51.2)	96 (52.2) 1 (0.5) 4 (2.2) 2 (1.1) 81 (44.0)	0.56
Stage	N (%) 3 3A 3B 3C	268	8 (9.5) 53 (63.1) 22 (26.2) 1 (1.2)	15 (8.2) 117 (63.6) 52 (28.3) 0 (0)	0.49
Course	N (%) 1 2 3 4	268	70 (83.3) 13 (15.5) 1 (1.2) 0 (0)	163 (88.6) 14 (7.6) 4 (2.2) 3 (1.6)	0.15
Treatment Intent	N (%) Curative	268	81 (96.4)	178 (96.7)	0.90
Technique	N (%) 3D Conformal Cyberknife IMRT VMAT	268	37 (44.1) 4 (4.8) 30 (35.7) 13 (15.5)	42 (22.8) 0 (0) 135 (73.4) 7 (3.8)	<0.001
RT Fractions	N (%) <30	268	53 (63.1)	17 (9.2)	<0.001
RT Dose	N (%) <6300	268	58 (69.1)	29 (15.8)	<0.001
Chemotherapy	N (%) Yes	268		184 (68.7)	
Chemotherapy	N (%) CISPETOP(RT) CISPPEME(RT) CISPVINO(RT) CRBPETOP(RT) CRBPPACL(RT)	268		151 (82.1) 6 (3.3) 2 (1.1) 22 (12.0) 3 (1.6)	
PET	N (%) =2	267	67 (79.8)	174 (95.1)	<0.001
Overall Survival, From Diagnosis	n (%) Censored Median (95% CI) Mos 1-year (95% CI) 3-year (95% CI)	268	32 (38.1) 18.1 (12.1, 24.9) 64.4 (51.6, 74.7) 24.3 (13.8, 36.4)	85 (46.2) 36.3 (28.9, 45.5) 82.5 (76.1, 87.4) 50.4 (42.1, 58.1)	<0.001
Overall Survival, From Start of RT	n (%) Censored Median (95% CI) Mos 1-year (95% CI) 3-year (95% CI)	268	32 (38.1) 15.2 (9.7, 22.7) 57.8 (44.8, 68.8) 22.4 (12.1, 34.7)	85 (46.2) 33.9 (26.2, 43.0) 77.7 (70.8, 83.2) 45.9 (37.5, 53.9)	<0.001

4.4.2 Survival

Survival from diagnosis was estimated for two groups of patients. Analysis of these two groups showed that the median survival of the RT alone group was 18.1 months (12.1, 24.9), 1-year survival was 64.4% (51.6, 74.7) and 3-year survival was 24.3% (13.8, 36.4). In the cCRT group the median survival of patients was 36.3 (28.9, 45.5) months, 1-year survival was 82.5% (76.1, 87.4), and 3-year survival was 50.4% (42.1, 58.1). The difference between the survival of these two groups was statistically significant. Figure 4.1 illustrates Kaplan – Meier curves of survival for the two groups.

Figure 4.1 Kaplan -Meier survival curve for Radiotherapy (RT) alone and Chemoradiation (Chemo-RT) groups.



4.4.3 Dosimetric Results

Table 4.2 Dosimetric Analysis of cCRT patients

	Unit		N	Chemo-Rad
N				**184**
Lung BLUNG-GTV Mean	Gy	Median (range)	172	12.9 (2.4, 22.7)
Lung 5 Gy	% Volume	Median (range)	210	48.5 (8.3, 76.9)
Lung 10 Gy	% Volume	Median (range)	208	34.1 (5.5, 56.6)
Lung 15 Gy	% Volume	Median (range)	209	27.1 (4.3, 44.4)
Lung 20 Gy	% Volume	Median (range)	209	23.4 (3.5, 37.3)
Esophagus 10 Gy	% Volume	Median (range)	189	48.3 (0.9, 93.0)
Esophagus 20 Gy	% Volume	Median (range)	189	37.4 (0, 83.9)
Esophagus 40 Gy	% Volume	Median (range)	189	24.2 (0, 69.0)
Esophagus Max	Gy	Median (range)	189	63.1 (15.9, 68.9)
Esophagus 5cc	Gy	Median (range)	189	47.5 (2.2, 63.7)
Esophagus Mean	Gy	Median (range)	189	19.6 (1.3, 43.9)
Heart 5 Gy	% Volume	Median (range)	207	29.7 (0, 99.6)
Heart 8 Gy	% Volume	Median (range)	208	26.0 (0, 98.5)
Heart 30 Gy	% Volume	Median (range)	207	7.5 (0, 63.6)
Heart 45 Gy	% Volume	Median (range)	165	1.2 (0, 9.6)
Heart Max	Gy	Median (range)	208	63.5 (0.4, 142.9)
Heart Mean	Gy	Median (range)	207	7.8 (0.2, 54.3)
GTV	cc	Median (range)	146	85.2 (11.1, 536.6)
PTV	cc	Median (range)	146	286.2 (59.4 (1054.2)

4.4.3.1 cCRT group

We were able to retrieve radiation plans in 146 out of 184 cases in this group. Most patients in the cCRT group were treated with similar dose and fractionation. The Median GTV volume was 85.2cc (11.1, 536.6), and the median PTV was 286.2cc (59.4, 1054)**.** Heart dose was reported at different constraint levels. Heart V5, V8, V30, V45, Max dose and Min dose were reported on each patient. On the cCRT group, the median of each constraint was Heart V5: 29.7cc, V8: 26cc, V30: 7.5cc, and V45: 1.2cc. Lung was the other constraint evaluated in this study. In the concurrent

chemoradiation group lung V5, V10, V15 and V20 were 12.9cc, 48.5cc, 34.1cc, 27.1cc and 23.4cc, respectively. The esophageal dosimetric evaluation showed that the median volume for V10, V20 and V40 were 48.3cc, 37.4cc and 24.2cc, respectively. The median of mean esophageal dose in this group of patients was 19.6Gy. The median value of the maximum esophageal dose was 63.1Gy. The median value for the 5cc volume of the esophagus was equal to 47.5Gy. **Table 4.2** shows the dosimetric analysis of cCRT.

4.4.3.2 RT group

Heart dose reported based on volume heart V5, V8, V30, and V45 were 21.2cc, 18.2cc, 3.1cc and 0, respectively. The heart maximum dose was calculated for each patient. Median heart max dose was 49.7 Gy. The heart mean dose was reported on each patient. Median heart mean dose was 5.1 Gy. **Table 4.3** shows the median of each dose constraints in RT alone group.

4.4.4 Cox Regression

In this analysis we have evaluated the association of variables with survival for all (RT-alone and cCRT-treated) patients together.

As shown in **Table 4.4**, our univariable Cox regression analysis demonstrated that age at registration, sex, stage, RT dose and the use of chemotherapy, Heart V5, V8, V30, and Heart mean dose were statistically significantly associated with survival. Female Sex [HR=0.71, 95%CI:0.52-0.99], higher RT dose [HR=0.69, 95%CI:0.5-0.97], the use of chemotherapy [HR=0.51, 95%CI:0.36-0.71] were significantly (p-value <0.05) associated with better survival.

Table 4.3 Dosimetric analysis of RT alone patients

	Unit		N	RT Only
N				**84**
Lung BL-GTV Mean	Gy	Median (range)	172	6.4 (0.9, 9.9)
Lung 5 Gy	% Volume	Median (range)	210	41.1 (2.9, 78.9)
Lung 10 Gy	% Volume	Median (range)	208	28.3 (1.9, 63.6)
Lung 15 Gy	% Volume	Median (range)	209	22.7 (1.1, 39.6)
Lung 20 Gy	% Volume	Median (range)	209	19.1 (0, 34.7)
Esophagus 10 Gy	% Volume	Median (range)	189	42.4 (0, 92.1)
Esophagus 20 Gy	% Volume	Median (range)	189	30.5 (0, 68.7)
Esophagus 40 Gy	% Volume	Median (range)	189	13.4 (0, 54.4)
Esophagus Max	Gy	Median (range)	189	49.9 (4.4, 65.4)
Esophagus 5cc	Gy	Median (range)	189	31.0 (0.9, 62.8)
Esophagus Mean	Gy	Median (range)	189	14.1 (0.3, 35.8)
Heart 5 Gy	% Volume	Median (range)	207	21.2 (0, 99.6)
Heart 8 Gy	% Volume	Median (range)	208	18.2 (0, 92.6)
Heart 30 Gy	% Volume	Median (range)	207	3.1 (0, 42.1)
Heart 45 Gy	% Volume	Median (range)	165	0 (0, 9.2)
Heart Max	Gy	Median (range)	208	49.7 (0.2, 69.0)
Heart Mean	Gy	Median (range)	207	5.1 (0.1, 43.4)
Cord D0.01	Gy	Median (range)	204	23.6 (1.3, 46.5)
GTV	cc	Median (range)	146	-
PTV	cc	Median (range)	146	-

Age [HR=1.02, 95%CI:1.00-1.04], Heart 5Gy [HR=1.01, 95%CI:1.00-1.01], Heart 8Gy [HR=1.01, 95%CI 1.00-1.02], Heat 30Gy [HR=1.02, 95%CI:1.01-1.03] and Heart mean dose [HR=1.03, 95%CI:1.01-1.05] were significantly (p-value <0.05) associated with worse survival.

Additionally, increasing stage subclasses were associated with worse survival [HR=0.08, 95% CI: 0.01-0.62 for stage III, HR=0.06, 95%CI:0.01-0.46 for stage IIIA, and HR=0.05, 95% CI:0.01-0.42 for stage IIIB versus stage IIIC as reference].

Table 4.4 Univariable and Multivariable Cox regression results for All patients.

Univariate Analysis		**Hazard Ratio (95% CI)**	**p-value**
Age at Registration	/ year	1.02 (1.00, 1.04)	0.019
Sex	F vs M	0.71 (0.52, 0.99)	0.041
Dx to RT, days	/ day	1.00 (0.99, 1.00)	0.19
Morphology	Adenocarcinoma Adenosquamous Carcinoma, NOS Large Cell Squamous Cell	0.68 (0.49, 0.95) 1.23 (0.17, 8.84) 0.53 (0.17, 1.69) 0.44 (0.06, 3.17) Reference	0.17
Stage	3 3A 3B 3C	0.08 (0.01, 0.62) 0.06 (0.01, 0.46) 0.05 (0.01, 0.42) Reference	0.034
Treatment Intent	Curative vs Palliative	0.67 (0.31, 1.44)	0.30
Technique	3D Conformal Cyberknife IMRT VMAT	1.20 (0.64, 2.25) 1.81 (0.40, 8.10) 0.92 (0.50, 1.68) Reference	0.40
RT Dose	<6300 vs >=6300	0.69 (0.50, 0.97)	0.031
Chemotherapy	Chemorads vs rads alone	0.51 (0.36, 0.71)	<0.001
Chemotherapy	CISPETOP(RT) CISPPEME(RT) CISPVINO(RT) CRBPETOP(RT) CRBPPACL(RT)	0.60 (0.15, 2.47) 0.26 (0.02, 2.88) NE 0.61 (0.13, 2.79) Reference	0.88
PET	1 vs 2	1.39 (0.83, 2.34)	0.21
Lung GTV Mean	/ unit	1.02 (0.98, 1.07)	0.39
Lung 5 Gy	/ unit	1.00 (0.99, 1.02)	0.50
Lung 10 Gy	/ unit	1.01 (0.99, 1.02)	0.49
Lung 15 Gy	/ unit	1.01 (0.99, 1.03)	0.39
Lung 20 Gy	/ unit	1.01 (0.99, 1.03)	0.34
Esophagus 10 Gy	/ unit	1.01 (1.00, 1.02)	0.19
Esophagus 20 Gy	/ unit	1.01 (1.00, 1.02)	0.31
Esophagus 40 Gy	/ unit	1.01 (1.00, 1.02)	0.15
Esophagus Max	/ unit	1.00 (0.99, 1.01)	0.73
Esophagus 5cc	/ unit	1.01 (1.00, 1.02)	0.094
Esophagus Mean	/ unit	1.02 (1.00, 1.04)	0.12
Heart 5 Gy	/ unit	1.01 (1.00, 1.01)	0.014
Heart 8 Gy	/ unit	1.01 (1.00, 1.02)	0.011
Heart 30 Gy	/ unit	1.02 (1.01, 1.03)	<0.001
Heart 45 Gy	/ unit	1.05 (0.97, 1.13)	0.21
Heart Max	/ unit	1.00 (0.99, 1.01)	0.59
Heart Mean	/ unit	1.03 (1.01, 1.05)	0.004
Cord D0.01	/ unit	1.00 (0.99, 1.02)	0.71
Multivariable Results			
Heart 5 Gy	/ unit	1.01 (1.00, 1.01)	0.010
Chemotherapy	Chemorad vs Rads alone	0.46 (0.31, 0.68)	<0.001

Interestingly, the time between diagnosis and RT, tumor histopathologic variants, radiation technique (3D conformal, IMRT and VMAT), chemotherapy type, PET utilization, lung dosimetric constraints, esophageal dosimetric constraints, Heart 45Gy volume, Heart Max and cord dose were not significantly associated with survival.

In multivariable analysis, Heart 5Gy volume (V5) was significantly associated with worse survival [HR=1.01, 95%CI:1.00, 1.01] (P = 0.010), and the use of chemotherapy was significantly (P<0.001) associated with better survival [HR=0.46, 95% CI: 0.31, 0.68]. **Table 4.4** shows the results of the Univariable and Multivariable Cox regression for all patients.

4.5 Discussion

Survival Data

This study aimed to evaluate the outcomes of two groups of patients with LA-NSCLC in an institutional setting and begin exploring tumor and RT parameters that may associate with, or determine survival outcomes.

Here we focused on patients treated with RT alone or with the standard of care of cCRT. One of the most striking findings in this study is that both the RT alone and the cCRT groups in this institutional series performed better than historical trial data and their contemporary average outcomes at the provincial level (Table 3.3, Chapter III).

The LHIN4 LA-NSCLC patients that received RT as their sole treatment had a median survival of 18.1 months, which appears outstanding when we compare the results to the historical radiation alone arms like in Dillmans study(57), which the median survival of the RT alone arm was 9.7 months. It has been three decades since that time, and a lot has changed, from better staging to better radiation treatment delivery. Likely all these parameters play a role in this improvement. The question of which factor played the major role is a debatable open question. Nevertheless, LHIN4 patients treated with RT alone seemed to have performed better than the average stage III patient in the province of Ontario that was treated with chest RT doses of 40Gy or higher (8.5-15.4 months, Table 3.3). This indicates a trend for improved performance of patients in this series.

However, stage III NSCLC patients treated with cCRT in LHIN4 also showed improved median OS compared to average patients in the province. As noted earlier, since cCRT has been the standard of care in almost every trial in the last decade, the improvement in survival of LA-

NSCLC patients in comparison with historical studies has been observed in almost every study. For example, median OS with standard cCRT, involving chest RT of 60Gy in 30 fractions, improved from 17 months in the Curran study(61) to 28.7 months, in the control arm of RTOG0617(75) and 27.1 months in the control arm of the PACIFIC trial(99). Interestingly, the median OS of our cCRT group reached 33.7 months, when calculated from the date of first RT fraction, or 36.3 months, when calculated from date of diagnosis. This is significantly higher than the provincial average (Table 3.3). It is possible that this may be a result of the fact that the majority of patient in these institutional cohort were staged and treated within an academic setting. Improved baseline assessments, such as mediastinal assessment, can lead to selection of improved performance status patients for treatment with increased RT dose over time.

The fact that here the effect size of improvement is lesser in the RT alone group than in the cCRT patients may be related to the heterogeneity of general health and baseline performance status in the RT alone patients. In this analysis, RT alone patients received a more heterogenous and generally lower total chest radiation dose and number of fractions compared to the cCRT dose and this could have influence outcomes. Although the provincial data found a survival benefit associated with radiation dose, recognizing the significant differences between the two groups discussed above, our intention is not to compare the RT alone outcomes against cCRT.

Certainly, improved staging leads to patient stage migration and contributes to outcomes. We have made efforts to explore the effect of PET in the staging and treatment delivery. A 79.8% of patients in RT alone group had PET compared to 95.1% of patients in the cCRT group. Integrating PET imaging into the diagnostic and therapeutic schema of lung cancer treatment took years, since PET was first approved by the Ontario Health Insurance Plan (OHIP) in 2009. We found that in our series only 26.2% of RT alone patients (22 out of 84 patients) had PET fused

with planning CT scans for radiation planning purposes, revealing that even though 79.8% had PET for staging, PET was systematically used for radiation planning only in a fraction of them. The integration of PET into treatment planning has taken many years. It is possible though that at early stages PET was indeed used to guide RT volume delineation but PET images were not fused with planning CT images. Since baseline metabolic tumor volume is suggested to have clinical value, accurate use of FDG-PET information during planning, which is achieved with PET fusion, should be utilized when possible.

Dosimetric Analysis Results

Radiotherapy dose was significantly associated with survival in univariant analysis. It should be noted that in our institutional data set patients received a consistent dose of radiation especially in the chemoradiation group. Use of PET was not associated with survival. This may not be surprising since most of the patients had PET for diagnostic purposes. Interestingly, in our analysis, lung and esophageal doses were also not associated with survival. This may be due to the fact that modern RT allows effective sparing of these organs form high dose RT and both dosimetrists and radiation oncologist made consistently strong efforts to limit radiation dose to these organs.

Debate on the connection between heart dose and survival in NSCLC patients has existed for years. Zhang et al. carried out a systematic review and meta-analysis, which aimed to evaluate the relevance between heart dose and survival in NSCLC patients. This systematic review failed to demonstrate consistent relationships among heart dose parameters, overall survival and heart events. For survival, only one of the 11 studies reported significant association with heart V5 in multivariable analysis and 2 of the 12 studies proposed significant association with heart V30; in

8 studies, mean heart dose was not statistically significant. For cardiotoxicity, heart V5 was significant by multivariable analysis in 1 of 2 studies; heart V30 was significant in 1 of 3 studies, and mean heart dose was significant in 2 of 4 studies (133).

Additionally, there is a controversy about the relationship between higher heart dose and poor survival rate in NSCLC patients. RTOG 0617 trial(78) reported that there is a significant relationship between higher heart dose and poor survival. Several studies have confirmed this correlation (79, 134), while others failed to verify this (135, 136).

Moreover, the effect of individual heart dose on survival is controversial. For example, several secondary analyses didn't report any significant correlation between heart dose and overall survival in NSCLC patients (137-140). However, in RTOG 0617, heart V5 and V30 were reported to have significant relationship with poor survival (78). Stam et al. reported clear correlations between heart V5/V30 and overall survival, but not heart V50 (134). Also, a significant association between heart V50 and survival was reported by Speirs et al.(79).

Importantly, in our study we found that increased Heart 5Gy, 8Gy, 30Gy, and Heart mean were significantly (p-value <0.05) associated with worse survival in univariable analysis, and this was true only for Heart 5Gy (V5) in multivariable analysis. These findings are consistent with other studies and indicate that more than one cardiac constraint parameter is important and no dose to the heart is safe. These results imply that clinicians should follow the role of as low as reasonably achievable (ALARA) dose to heart.

On the other hand, it seems necessary that future studies should focus further on overall normal tissue toxicity models that take more than one tissue into consideration. These new models include dose-volume characteristics from multiple cardiopulmonary substructures (atria, lung, pericardium, and ventricles) as well as tumor and individual characteristics to quantitatively

predict the impact of cardiopulmonary dose on overall survival after radiotherapy of LA-NSCLC patients. These new models have a strong ability to discriminate risk and could be used in treatment planning to reduce mortality risk through adjustment of dose patterns outside the tumor volume (132, 138).

Weaknesses of dosimetric analysis

Dosimetric analysis in this study should be interpreted with caution. To improve the statistical power of the analysis of dosimetric variables, we performed the initial analysis of our data by combining results from the RT alone and cCRT groups. Although combining these groups could provide statistical strength and give a general perspective at the dosimetric level, there are caveats with such a combined analysis. More than 90% of the cCRT patients received a radiation dose of more than 60 Gy, while 70% of RT alone patients received a radiation dose of less than 60 Gy. Evidently, on every dose constraint, the RT alone patients received an average lower dose to the organs at risk. Another approach is to pursue this analysis is to evaluate the association of dosimetric parameters with outcomes separately in each group. This is certainly our plan for the future further analysis of our institutional data. An additional reason that makes such an analysis important is the fact that patients treated with cCRT receive two cytotoxic therapies during treatment (RT+chemotherapy) and this certainly influences the impact of RT toxicity on normal tissues.

Finally, it should be recognized that there are inherited risks associated with the overall type of analysis we performed here. The retrospective nature of the study, the inability to control different intervening factors like performance status level, smoking status and weight loss are setbacks in our study.

5.0. Overall Summary and Conclusions

The first aim of this study was to determine the survival outcomes of RT in well-staged patients with LA-NSCLC treated in a North American setting, as well as evaluate the role of RT dose and modern staging with FDG-PET on the overall survival. Secondly, tumor and RT dosimetric parameters were analyzed to evaluate the association with survival outcomes in LA-NSCLC patients. To achieve these aims, we did a retrospective analysis in the provincial (Ontario) and the regional institutional (Ontario LHIN4) (Juravinski and Walker Family Cancer Centers) settings.

The population-based study allowed us to make some significant observations. Although our approach to selected well-staged patients with unresected stage III NSCLC resulted in elimination of a significant number of patients from our analysis, we observed interesting trends in the utilization of RT alone, as a sole treatment modality, compared to the use of SOC cCRT and and sCRT. It appears that RT monotherapy remains a widely used treatment in LA-NSCLC (used in just under 40% of patients), while the SOC of cCRT in used is less than half of stage III patients. Although there may be a clinically valid rationale for treatment selection, this finding has important implications in terms of the appropriate utilization of SOC in our province. This is also important in terms of utilization of the recently established SOC in stage III that includes use of adjuvant immune checkpoint inhibitor therapy for which patients are eligible only after completion of cCRT.

Importantly, in this study we found that higher RT dose and PET utilization were independently associated with improved survival in multivariate analysis. This observation is valid for all patients and applied to both patients treated with RT alone and those treated with the SOC

of cCRT. It indicates that clinicians should consider utilization of FDG-PET in all patients treated with RT. Curative dose chest RT should be appropriately considered not only in patients receiving the SOC of cCRT but also in those treated with RT alone. Overall, these findings and the observed survival outcomes of patients treated with RT alone indicate that this group of patients is an important population that deserves further systematic study.

The primary aim of our institutional analysis was to identify well-staged patients that received definitive chest RT for the treatment of stage III NSCLC, in order to investigate whether dosimetric parameters can determine survival outcomes. Unexpectedly, the survival analysis of our regional (LHIN4) data yielded outcomes that are clearly improved compared to provincial observations and reported multi-institutional randomized trials. Although, the reasons for these observations may be multi-factorial, these results suggest that our institutional cohort is indeed an appropriate group of patients to investigate whether of RT treatment dosimetric parameters influence survival outcomes of modern radiotherapy in LA-NSCLC.

The clinical and dosimetric evaluation showed that gender, RT dose and the use of chemotherapy were significantly associated with better survival. Age, Heart 5Gy, 8Gy, 30Gy, Heart mean dose and increasing stage subclasses were significantly associated with worse survival. In multivariable analysis, Heart 5Gy volume was associated with worse survival, and the use of chemotherapy was associated with better survival.

Dosimetric constraints play a key role in the survival of every patient receiving radiotherapy; higher tumor dose and lesser heart dose seem vital in all these patients. Given the potential survival detriment detected with irradiation of the heart, clinicians should make efforts to utilize modern high precision planning and radiotherapy delivery techniques to spare treatment of normal tissues in all patients who are candidates of either RT alone or SOC cCRT treatment.

Impact of this work on clinical investigation in LA-NSCLC

Overall, the findings of this work allow us to conclude that,

I) There are clear improvements in the survival outcomes of RT in unresected LA-NSCLC.

II) A significant portion of patients continue to receive RT, as a sole treatment modality and future clinical trials should include investigation of this population.

III) Use of curative dose RT and use of FDG-PET should be strongly considered in all patients with unresectable stage III NSCLC.

IV) Strong efforts should be made to reduce irradiation of the heart when chest RT is given for the treatment of NSCLC. Reduction of treatment of the heart with any dose rather than achieving satisfaction of a single dosimetric constraint may be the best approach to avoid cardiac toxicity and help improve survival in patients with LA-NSCLC treated with RT.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.
2. Canada S. 2022 [Available from: https://www.statcan.gc.ca/o1/en/plus/238-lung-cancer-leading-cause-cancer-death-canada.
3. Bradley SH, Kennedy MPT, Neal RD. Recognising Lung Cancer in Primary Care. Adv Ther. 2019;36(1):19-30.
4. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e1S-e29S.
5. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009;10(11):1033-4.
6. Taylor R, Najafi F, Dobson A. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. Int J Epidemiol. 2007;36(5):1048-59.
7. Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risks Hum. 2012;100(Pt C):11-465.
8. Driscoll T, Nelson DI, Steenland K, Leigh J, Concha-Barrientos M, Fingerhut M, et al. The global burden of disease due to occupational carcinogens. Am J Ind Med. 2005;48(6):419-31.
9. Roberts KE, Hamele-Bena D, Saqi A, Stein CA, Cole RP. Pulmonary tumor embolism: a review of the literature. Am J Med. 2003;115(3):228-32.
10. Morales-Oyarvide V, Mino-Kenudson M. Tumor islands and spread through air spaces: Distinct patterns of invasion in lung adenocarcinoma. Pathol Int. 2016;66(1):1-7.
11. Lababede O, Meziane MA. The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams. Oncologist. 2018;23(7):844-8.
12. Kim AW. Lymph node drainage patterns and micrometastasis in lung cancer. Semin Thorac Cardiovasc Surg. 2009;21(4):298-308.
13. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017;151(1):193-203.
14. Onuigbo WIB. A mono-block formalin-fixation method for investigating cancer metastasis. Zeitschrift für Krebsforschung. 1963;65(3):209-10.
15. Trillet V, Catajar JF, Croisile B, Turjman F, Aimard G, Bourrat C, et al. Cerebral metastases as first symptom of bronchogenic carcinoma. A prospective study of 37 cases. Cancer. 1991;67(11):2935-40.
16. Aberle DR, Berg CD, Black WC, Church TR, Fagerstrom RM, Galen B, et al. The National Lung Screening Trial: overview and study design. Radiology. 2011;258(1):243-53.
17. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e211S-e50S.

18. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011;6(2):244-85.
19. Lam VK, Tran HT, Banks KC, Lanman RB, Rinsurongkawong W, Peled N, et al. Targeted Tissue and Cell-Free Tumor DNA Sequencing of Advanced Lung Squamous-Cell Carcinoma Reveals Clinically Significant Prevalence of Actionable Alterations. Clin Lung Cancer. 2019;20(1):30-6.e3.
20. Rekhtman N, Ang DC, Sima CS, Travis WD, Moreira AL. Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. Mod Pathol. 2011;24(10):1348-59.
21. Mukhopadhyay S, Katzenstein AL. Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: Utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6. Am J Surg Pathol. 2011;35(1):15-25.
22. Terry J, Leung S, Laskin J, Leslie KO, Gown AM, Ionescu DN. Optimal immunohistochemical markers for distinguishing lung adenocarcinomas from squamous cell carcinomas in small tumor samples. Am J Surg Pathol. 2010;34(12):1805-11.
23. Rami-Porta R, Bolejack V, Giroux DJ, Chansky K, Crowley J, Asamura H, et al. The IASLC lung cancer staging project: the new database to inform the eighth edition of the TNM classification of lung cancer. J Thorac Oncol. 2014;9(11):1618-24.
24. Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015;10(7):990-1003.
25. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015;10(12):1675-84.
26. Detterbeck FC, Chansky K, Groome P, Bolejack V, Crowley J, Shemanski L, et al. The IASLC Lung Cancer Staging Project: Methodology and Validation Used in the Development of Proposals for Revision of the Stage Classification of NSCLC in the Forthcoming (Eighth) Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2016;11(9):1433-46.
27. Eberhardt WE, Mitchell A, Crowley J, Kondo H, Kim YT, Turrisi A, 3rd, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revision of the M Descriptors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2015;10(11):1515-22.
28. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39-51.
29. Nicholson AG, Chansky K, Crowley J, Beyruti R, Kubota K, Turrisi A, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(3):300-11.

30. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014;64(4):252-71.
31. Canadian Cancer Society. Survival statistics for non-small cell lung cancer 2020 [Available from: https://cancer.ca/en/cancer-information/cancer-types/lung/prognosis-and-survival/non-small-cell-lung-cancer-survival-statistics.
32. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363(18):1693-703.
33. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2018;379(21):2027-39.
34. Shaw AT, Bauer TM, de Marinis F, Felip E, Goto Y, Liu G, et al. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. N Engl J Med. 2020;383(21):2018-29.
35. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(9):829-38.
36. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371(23):2167-77.
37. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327-34.
38. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239-46.
39. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11(2):121-8.
40. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015;16(2):141-51.
41. Mazieres J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol. 2019;30(8):1321-8.
42. Ferrara R, Auger N, Auclin E, Besse B. Clinical and Translational Implications of RET Rearrangements in Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(1):27-45.
43. Michels S, Scheel AH, Scheffler M, Schultheis AM, Gautschi O, Aebersold F, et al. Clinicopathological Characteristics of RET Rearranged Lung Cancer in European Patients. J Thorac Oncol. 2016;11(1):122-7.
44. Mazières J, Zalcman G, Crinò L, Biondani P, Barlesi F, Filleron T, et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. J Clin Oncol. 2015;33(9):992-9.

45. Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2014;371(21):1963-71.
46. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379(24):2342-50.
47. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387(10030):1837-46.
48. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019;381(21):2020-31.
49. Lutz ST, Jones J, Chow E. Role of radiation therapy in palliative care of the patient with cancer. J Clin Oncol. 2014;32(26):2913-9.
50. McAvoy S, Ciura K, Wei C, Rineer J, Liao Z, Chang JY, et al. Definitive reirradiation for locoregionally recurrent non-small cell lung cancer with proton beam therapy or intensity modulated radiation therapy: predictors of high-grade toxicity and survival outcomes. Int J Radiat Oncol Biol Phys. 2014;90(4):819-27.
51. Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg. 2011;141(3):662-70.
52. Lee PC, Nasar A, Port JL, Paul S, Stiles B, Chiu YL, et al. Long-term survival after lobectomy for non-small cell lung cancer by video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg. 2013;96(3):951-60; discussion 60-1.
53. Perez CA, Stanley K, Rubin P, Kramer S, Brady L, Perez-Tamayo R, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. Cancer. 1980;45(11):2744-53.
54. Trovó MG, Minatel E, Franchin G, Boccieri MG, Nascimben O, Bolzicco G, et al. Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 1992;24(1):11-5.
55. Morton RF, Jett JR, McGinnis WL, Earle JD, Therneau TM, Krook JE, et al. Thoracic radiation therapy alone compared with combined chemoradiotherapy for locally unresectable non-small cell lung cancer. A randomized, phase III trial. Ann Intern Med. 1991;115(9):681-6.
56. Mattson K, Holsti LR, Holsti P, Jakobsson M, Kajanti M, Liippo K, et al. Inoperable non-small cell lung cancer: radiation with or without chemotherapy. Eur J Cancer Clin Oncol. 1988;24(3):477-82.
57. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med. 1990;323(14):940-5.
58. Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst. 1991;83(6):417-23.

59. Sause W, Kolesar P, Taylor SI, Johnson D, Livingston R, Komaki R, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest. 2000;117(2):358-64.
60. Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med. 1992;326(8):524-30.
61. Curran WJ, Jr., Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103(19):1452-60.
62. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol. 1999;17(9):2692-9.
63. Atagi S, Kawahara M, Yokoyama A, Okamoto H, Yamamoto N, Ohe Y, et al. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). Lancet Oncol. 2012;13(7):671-8.
64. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA: a cancer journal for clinicians. 2021;71(1):7-33.
65. Islam KM, Jiang X, Anggondowati T, Lin G, Ganti AK. Comorbidity and Survival in Lung Cancer Patients. Cancer Epidemiol Biomarkers Prev. 2015;24(7):1079-85.
66. Janssen-Heijnen ML, Schipper RM, Razenberg PP, Crommelin MA, Coebergh JW. Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study. Lung Cancer. 1998;21(2):105-13.
67. Scagliotti GV, Parikh P, Pawel Jv, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non–Small-Cell Lung Cancer. Journal of Clinical Oncology. 2008;26(21):3543-51.
68. Senan S, Brade A, Wang L-h, Vansteenkiste J, Dakhil S, Biesma B, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non–Small-Cell Lung Cancer. Journal of Clinical Oncology. 2016;34(9):953-62.
69. Bradley JD, Moughan J, Graham MV, Byhardt R, Govindan R, Fowler J, et al. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell lung cancer: phase I results of RTOG 0117. Int J Radiat Oncol Biol Phys. 2010;77(2):367-72.
70. Bradley JD, Bae K, Graham MV, Byhardt R, Govindan R, Fowler J, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. J Clin Oncol. 2010;28(14):2475-80.
71. Schild SE, McGinnis WL, Graham D, Hillman S, Fitch TR, Northfelt D, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2006;65(4):1106-11.

72. Socinski MA, Blackstock AW, Bogart JA, Wang X, Munley M, Rosenman J, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol. 2008;26(15):2457-63.
73. Stinchcombe TE, Lee CB, Moore DT, Rivera MP, Halle J, Limentani S, et al. Long-term follow-up of a phase I/II trial of dose escalating three-dimensional conformal thoracic radiation therapy with induction and concurrent carboplatin and paclitaxel in unresectable stage IIIA/B non-small cell lung cancer. J Thorac Oncol. 2008;3(11):1279-85.
74. Machtay M, Bae K, Movsas B, Paulus R, Gore EM, Komaki R, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 2012;82(1):425-34.
75. Bradley JD, Hu C, Komaki RR, Masters GA, Blumenschein GR, Schild SE, et al. Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non-Small-Cell Lung Cancer. J Clin Oncol. 2020;38(7):706-14.
76. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187-99.
77. Yom SS, Liao Z, Liu HH, Tucker SL, Hu CS, Wei X, et al. Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2007;68(1):94-102.
78. Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. J Clin Oncol. 2017;35(1):56-62.
79. Speirs CK, DeWees TA, Rehman S, Molotievschi A, Velez MA, Mullen D, et al. Heart Dose Is an Independent Dosimetric Predictor of Overall Survival in Locally Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2017;12(2):293-301.
80. Nestle U, De Ruysscher D, Ricardi U, Geets X, Belderbos J, Pöttgen C, et al. ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer. Radiother Oncol. 2018;127(1):1-5.
81. Bradley J, Thorstad WL, Mutic S, Miller TR, Dehdashti F, Siegel BA, et al. Impact of FDG-PET on radiation therapy volume delineation in non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2004;59(1):78-86.
82. Nestle U, Walter K, Schmidt S, Licht N, Nieder C, Motaref B, et al. 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: high impact in patients with atelectasis. Int J Radiat Oncol Biol Phys. 1999;44(3):593-7.
83. van Der Wel A, Nijsten S, Hochstenbag M, Lamers R, Boersma L, Wanders R, et al. Increased therapeutic ratio by 18FDG-PET CT planning in patients with clinical CT stage N2-

N3M0 non-small-cell lung cancer: a modeling study. Int J Radiat Oncol Biol Phys. 2005;61(3):649-55.
84. Ceresoli GL, Cattaneo GM, Castellone P, Rizzos G, Landoni C, Gregorc V, et al. Role of computed tomography and [18F] fluorodeoxyglucose positron emission tomography image fusion in conformal radiotherapy of non-small cell lung cancer: a comparison with standard techniques with and without elective nodal irradiation. Tumori. 2007;93(1):88-96.
85. Faria SL, Menard S, Devic S, Sirois C, Souhami L, Lisbona R, et al. Impact of FDG-PET/CT on radiotherapy volume delineation in non-small-cell lung cancer and correlation of imaging stage with pathologic findings. Int J Radiat Oncol Biol Phys. 2008;70(4):1035-8.
86. Yin LJ, Yu XB, Ren YG, Gu GH, Ding TG, Lu Z. Utilization of PET-CT in target volume delineation for three-dimensional conformal radiotherapy in patients with non-small cell lung cancer and atelectasis. Multidiscip Respir Med. 2013;8(1):21.
87. Fischer B, Lassen U, Mortensen J, Larsen S, Loft A, Bertelsen A, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med. 2009;361(1):32-9.
88. Ung Y, Gu C, Cline K, Sun A, MacRae RM, Wright JR, et al. An Ontario Clinical Oncology Group (OCOG) randomized trial (PET START) of FDG PET/CT in patients with stage III non-small cell lung cancer (NSCLC): Predictors of overall survival. Journal of Clinical Oncology. 2011;29(15_suppl):7018-.
89. Machtay M, Duan F, Siegel BA, Snyder BS, Gorelick JJ, Reddin JS, et al. Prediction of survival by [18F]fluorodeoxyglucose positron emission tomography in patients with locally advanced non-small-cell lung cancer undergoing definitive chemoradiation therapy: results of the ACRIN 6668/RTOG 0235 trial. J Clin Oncol. 2013;31(30):3823-30.
90. Bradley J, Bae K, Choi N, Forster K, Siegel BA, Brunetti J, et al. A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of Radiation Therapy Oncology Group (RTOG) 0515. Int J Radiat Oncol Biol Phys. 2012;82(1):435-41.e1.
91. Kong F-MS, Hu C, Haken RT, Xiao Y, Matuszak M, Hirsh V, et al. NRG-RTOG 1106/ACRIN 6697: A phase IIR trial of standard versus adaptive (mid-treatment PET-based) chemoradiotherapy for stage III NSCLC—Results and comparison to NRG-RTOG 0617 (non-personalized RT dose escalation). Journal of Clinical Oncology. 2021;39(15_suppl):8548-.
92. S. Yuan, 2, Q. Yu, 3, S. Wang, 3 , Y. Xu, 5 , H. Ge J, Wang, et al. Individualized Adaptive Radiotherapy versus Standard Radiotherapy with Chemotherapy for Patients with Locally Advanced Non-Small Cell Lung Cancer: A Multicenter Randomized Phase III Clinical Trial CRTOG1601. Int J Radiat Oncol Biol Phys 2020;108(3).
93. Blumenschein GR, Jr., Paulus R, Curran WJ, Robert F, Fossella F, Werner-Wasik M, et al. Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. J Clin Oncol. 2011;29(17):2312-8.
94. Choong NW, Mauer AM, Haraf DJ, Lester E, Hoffman PC, Kozloff M, et al. Phase I trial of erlotinib-based multimodality therapy for inoperable stage III non-small cell lung cancer. J Thorac Oncol. 2008;3(9):1003-11.
95. Govindan R, Bogart J, Stinchcombe T, Wang X, Hodgson L, Kratzke R, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol. 2011;29(23):3120-5.

96. Kelly K, Chansky K, Gaspar LE, Jett JR, Ung Y, Albain KS, et al. Updated analysis of SWOG 0023: A randomized phase III trial of gefitinib versus placebo maintenance after definitive chemoradiation followed by docetaxel in patients with locally advanced stage III non-small cell lung cancer. Journal of Clinical Oncology. 2007;25(18_suppl):7513-.
97. Ready N, Jänne PA, Bogart J, Dipetrillo T, Garst J, Graziano S, et al. Chemoradiotherapy and gefitinib in stage III non-small cell lung cancer with epidermal growth factor receptor and KRAS mutation analysis: cancer and leukemia group B (CALEB) 30106, a CALGB-stratified phase II trial. J Thorac Oncol. 2010;5(9):1382-90.
98. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(20):1919-29.
99. Antonia SJ. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379(24):2342-50.
100. Tsakiridis T, Hu C, Skinner HD, Santana-Davila R, Lu B, Erasmus JJ, et al. Initial reporting of NRG-LU001 (NCT02186847), randomized phase II trial of concurrent chemoradiotherapy (CRT) +/- metformin in locally advanced Non-Small Cell Lung Cancer (NSCLC). Journal of Clinical Oncology. 2019;37(15_suppl):8502-.
101. Tsakiridis T, Pond GR, Wright J, Ellis PM, Ahmed N, Abdulkarim B, et al. Metformin in Combination With Chemoradiotherapy in Locally Advanced Non-Small Cell Lung Cancer: The OCOG-ALMERA Randomized Clinical Trial. JAMA Oncol. 2021;7(9):1333-41.
102. MacManus MP, Hicks RJ, Matthews JP, Hogg A, McKenzie AF, Wirth A, et al. High rate of detection of unsuspected distant metastases by pet in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. Int J Radiat Oncol Biol Phys. 2001;50(2):287-93.
103. Liu HH, Balter P, Tutt T, Choi B, Zhang J, Wang C, et al. Assessing respiration-induced tumor motion and internal target volume using four-dimensional computed tomography for radiotherapy of lung cancer. Int J Radiat Oncol Biol Phys. 2007;68(2):531-40.
104. Franceschini D, De Rose F, Cozzi L, Navarria P, Clerici E, Franzese C, et al. Radical hypo-fractionated radiotherapy with volumetric modulated arc therapy in lung cancer : A retrospective study of elderly patients with stage III disease. Strahlenther Onkol. 2017;193(5):385-91.
105. Joo JH, Song SY, Kim SS, Jeong Y, Jeong SY, Choi W, et al. Definitive radiotherapy alone over 60 Gy for patients unfit for combined treatment to stage II-III non-small cell lung cancer: retrospective analysis. Radiat Oncol. 2015;10:250.
106. Wang L, Correa CR, Zhao L, Hayman J, Kalemkerian GP, Lyons S, et al. The effect of radiation dose and chemotherapy on overall survival in 237 patients with Stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2009;73(5):1383-90.
107. Guo M, Li B, Yu Y, Wang S, Xu Y, Sun X, et al. Delineating the pattern of treatment for elderly locally advanced NSCLC and predicting outcomes by a validated model: A SEER based analysis. Cancer Med. 2019;8(5):2587-98.
108. Sigel K, Lurslurchachai L, Bonomi M, Mhango G, Bergamo C, Kale M, et al. Effectiveness of radiation therapy alone for elderly patients with unresected stage III non-small cell lung cancer. Lung Cancer. 2013;82(2):266-70.

109. Iocolano M, Wild AT, Hannum M, Zhang Z, Simone CB, 2nd, Gelblum D, et al. Hypofractionated vs. conventional radiation therapy for stage III non-small cell lung cancer treated without chemotherapy. Acta Oncol. 2020;59(2):164-70.
110. Seung SJ, Hurry M, Walton RN, Evans WK. Retrospective cohort study of unresectable stage III non-small-cell lung cancer in Canada. Curr Oncol. 2020;27(4):e354-e60.
111. Miller ED, Fisher JL, Haglund KE, Grecula JC, Xu-Welliver M, Bertino EM, et al. The Addition of Chemotherapy to Radiation Therapy Improves Survival in Elderly Patients with Stage III Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(3):426-35.
112. Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. Update of Incidence, Prevalence, Survival, and Initial Treatment in Patients With Non-Small Cell Lung Cancer in the US. JAMA Oncol. 2021;7(12):1824-32.
113. Ramalingam S, Belani C. Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions. Oncologist. 2008;13 Suppl 1:5-13.
114. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379(24):2342-50.
115. Moore S, Leung B, Wu J, Ho C. Real-World Treatment of Stage III NSCLC: The Role of Trimodality Treatment in the Era of Immunotherapy. J Thorac Oncol. 2019;14(8):1430-9.
116. Vinod SK, Wai E, Alexander C, Tyldesley S, Murray N. Stage III non-small-cell lung cancer: population-based patterns of treatment in British Columbia, Canada. J Thorac Oncol. 2012;7(7):1155-63.
117. Yusuf D, Walton RN, Hurry M, Farrer C, Bebb DG, Cheung WY. Population-based Treatment Patterns and Outcomes for Stage III Non-Small Cell Lung Cancer Patients: A Real-world Evidence Study. Am J Clin Oncol. 2020;43(9):615-20.
118. Peng J, Pond G, Donovan E, Ellis PM, Swaminath A. A Comparison of Radiation Techniques in Patients Treated With Concurrent Chemoradiation for Stage III Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2020;106(5):985-92.
119. Cheng M, Jolly S, Quarshie WO, Kapadia N, Vigneau FD, Kong FS. Modern Radiation Further Improves Survival in Non-Small Cell Lung Cancer: An Analysis of 288,670 Patients. J Cancer. 2019;10(1):168-77.
120. Taus Á, Aguiló R, Curull V, Suárez-Piñera M, Rodríguez-Fuster A, Rodríguez de Dios N, et al. Impact of 18F-FDG PET/CT in the treatment of patients with non-small cell lung cancer. Arch Bronconeumol. 2014;50(3):99-104.
121. Iyengar P, Zhang-Velten E, Court L, Westover K, Yan Y, Lin MH, et al. Accelerated Hypofractionated Image-Guided vs Conventional Radiotherapy for Patients With Stage II/III Non-Small Cell Lung Cancer and Poor Performance Status: A Randomized Clinical Trial. JAMA Oncol. 2021;7(10):1497-505.
122. Skinner H, Hu C, Tsakiridis T, Santana-Davila R, Lu B, Erasmus JJ, et al. Addition of Metformin to Concurrent Chemoradiation in Patients With Locally Advanced Non-Small Cell Lung Cancer: The NRG-LU001 Phase 2 Randomized Clinical Trial. JAMA Oncol. 2021;7(9):1324-32.
123. Vokes EE, Govindan R, Iscoe N, Hossain AM, San Antonio B, Chouaki N, et al. The Impact of Staging by Positron-Emission Tomography on Overall Survival and Progression-Free Survival in Patients With Locally Advanced NSCLC. J Thorac Oncol. 2018;13(8):1183-8.

124. Berberoğlu K. Use of Positron Emission Tomography/Computed Tomography in Radiation Treatment Planning for Lung Cancer. Mol Imaging Radionucl Ther. 2016;25(2):50-62.
125. Ambroggi M, Biasini C, Del Giovane C, Fornari F, Cavanna L. Distance as a Barrier to Cancer Diagnosis and Treatment: Review of the Literature. The oncologist. 2015;20(12):1378-85.
126. Koo TR, Moon SH, Lim YJ, Kim JY, Kim Y, Kim TH, et al. The effect of tumor volume and its change on survival in stage III non-small cell lung cancer treated with definitive concurrent chemoradiotherapy. Radiation Oncology. 2014;9(1):283.
127. Karin M, Taugner J, Käsmann L, Eze C, Roengvoraphoj O, Tufman A, et al. Association of Planning Target Volume with Patient Outcome in Inoperable Stage III NSCLC Treated with Chemoradiotherapy: A Comprehensive Single-Center Analysis. Cancers (Basel). 2020;12(10).
128. Shen L, Liu C, Jin J, Han C, Zhou Y, Zheng X, et al. Association of lung and heart dose with survival in patients with non-small cell lung cancer underwent volumetric modulated arc therapy. Cancer Manag Res. 2019;11:6091-8.
129. Belderbos J, Heemsbergen W, Hoogeman M, Pengel K, Rossi M, Lebesque J. Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. Radiother Oncol. 2005;75(2):157-64.
130. Cox JD, Pajak TF, Asbell S, Russell AH, Pederson J, Byhardt RW, et al. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. Int J Radiat Oncol Biol Phys. 1993;27(3):493-8.
131. Badiyan SN, Robinson CG, Bradley JD. Radiation Toxicity in Lung Cancer Patients: The Heart of the Problem? Int J Radiat Oncol Biol Phys. 2019;104(3):590-2.
132. Thor M, Deasy JO, Hu C, Gore E, Bar-Ad V, Robinson C, et al. Modeling the Impact of Cardiopulmonary Irradiation on Overall Survival in NRG Oncology Trial RTOG 0617. Clin Cancer Res. 2020;26(17):4643-50.
133. Zhang TW, Snir J, Boldt RG, Rodrigues GB, Louie AV, Gaede S, et al. Is the Importance of Heart Dose Overstated in the Treatment of Non-Small Cell Lung Cancer? A Systematic Review of the Literature. Int J Radiat Oncol Biol Phys. 2019;104(3):582-9.
134. Stam B, van der Bijl E, van Diessen J, Rossi MMG, Tijhuis A, Belderbos JSA, et al. Heart dose associated with overall survival in locally advanced NSCLC patients treated with hypofractionated chemoradiotherapy. Radiother Oncol. 2017;125(1):62-5.
135. Tucker SL, Liu A, Gomez D, Tang LL, Allen P, Yang J, et al. Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation. Radiother Oncol. 2016;119(3):495-500.
136. McWilliam A, Kennedy J, Hodgson C, Vasquez Osorio E, Faivre-Finn C, van Herk M. Radiation dose to heart base linked with poorer survival in lung cancer patients. Eur J Cancer. 2017;85:106-13.
137. Wang K, Eblan MJ, Deal AM, Lipner M, Zagar TM, Wang Y, et al. Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. J Clin Oncol. 2017;35(13):1387-94.
138. Guberina M, Eberhardt W, Stuschke M, Gauler T, Heinzelmann F, Cheufou D, et al. Heart dose exposure as prognostic marker after radiotherapy for resectable stage IIIA/B non-small-cell lung cancer: secondary analysis of a randomized trial. Ann Oncol. 2017;28(5):1084-9.

139. Dess RT, Sun Y, Matuszak MM, Sun G, Soni PD, Bazzi L, et al. Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2017;35(13):1395-402.
140. Wang K, Pearlstein KA, Patchett ND, Deal AM, Mavroidis P, Jensen BC, et al. Heart dosimetric analysis of three types of cardiac toxicity in patients treated on dose-escalation trials for Stage III non-small-cell lung cancer. Radiother Oncol. 2017;125(2):293-300.