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INNOVATIVE MEDICINE **Best Practices**

Treatment of Unresectable Stage III Non-small Cell Lung Cancer

Introduction

With a recent renaissance in cancer diagnostics and treatment, there is renewed promise for many who previously held little hope. Lung cancer represents the second most frequently diagnosed cancer, a close second to breast cancer, at 12.9% of expected new cancer cases in 2019.[1] However, the 23.5% death rate predicted for lung cancer outranks breast, prostate, colorectal, and skin melanomas combined.[1] Five-year lung cancer survival rates have increased from 11% in 1975 to more than 20% in 2016.[1] This relatively low rate of survival can probably be explained by the fact that the majority of patients are diagnosed with locally advanced disease (Stage III, disease metastatic to mediastinal or supraclavicular nodes) or advanced disease (Stage IV, disease metastatic to other organs).[2-4] Recent advancements in treatment are proving effective in improving patient outcomes[5,6]; combined with adherence to screening recommendations and immediate referral to appropriate specialists, earlier diagnosis and staging can help lead to improved outcomes.[7-9]

Non-small cell lung cancer (NSCLC) constitutes 80% to 85% of lung cancer diagnoses, including histological identification of adenocarcinoma, squamous cell, large cell, and undifferentiated carcinomas.[10-12] Approximately 25% to 30% of patients with NSCLC are diagnosed with locally advanced or Stage III disease.[12] A proportion of these patients may experience the curative benefits of combined chemotherapy and surgery or concurrent chemotherapy and radiation therapy.[5,13] About 40% of patients with NSCLC are diagnosed with Stage IV disease, and the treatment goal in these patients is to manage symptoms, improve quality of life, and extend survival.[13,14] Treatment options include systemic chemotherapy, targeted mutation therapies, radiation, immunotherapy, and on occasion surgery.[7] It is vital that we increase early diagnosis, accurate staging, and referral to the appropriate specialists in lung cancer to ensure that treatment is optimized and more lives are potentially saved.[7]

Screening and Diagnosis

Unlike with breast, prostate, and colorectal cancers, systematic screening for lung cancer is not a well-established population-based practice, and its role is not fully grasped by primary caregivers.[15] Risk factors such as history of tobacco use and exposure to second-hand smoke are common knowledge, but other environmental exposures (diesel smoke, pollution, and other cancer-causing agents) are difficult to quantify.[16,17] Populations with lifestyles with higher exposure to these factors are generally more reticent to intervention and skeptical of the benefits of treatment, while others may be concerned that radiation-based screening techniques contribute to the risk.[15] In addition to patient perceptions that defer intervention, presenting symptoms of cough and dyspnea are frequently confounded with other respiratory conditions, creating a delay in early detection and staging.[9] Even further delays have been seen when patients present with more generalized symptoms like fatigue or bone or joint pain.[9]

Based on the National Lung Screening Trial (NLST),[18] the American College of Chest Physicians (ACCP) has published recommendations that low-dose computerized tomography (LDCT) scans be performed annually on patients meeting the following criteria: (1) 30 pack-year current smoker or former smoker between the ages of 55 and 74 years, (2) former smokers who have quit within the past 15 years, and (3) no comorbidities that potentially preclude curative treatment benefit.[15] The National Comprehensive Cancer Network® (NCCN®) also encourages patients to seek yearly screening if they are 50 years or older, have a 20 or more pack-year smoking history, and have other known risk factors besides second-hand smoke exposure, such as radon exposure.[19] Screening with LDCT, in select patients at high risk for lung cancer, decreased the relative risk of death from lung cancer by 20% when compared with chest radiography.[18] As such, efforts are being made to educate general practitioners and the public about this tremendous benefit.[15,19,20]

The goal of screening is to identify a lung cancer in the earliest possible stage, which, as **Table 1** demonstrates, directly improves survivability.[19] However, imaging alone does not provide accurate staging, and once lung cancer is suspected, time is of the essence in ensuring no further progression. Various target time recommendations have been published advocating for improved wait times across the care spectrum, ranging from 30 to 52 days of median wait time from diagnosis to first treatment.[23,24] Yet one Canadian study showed that despite the recommended time of 2 weeks between symptom onset and diagnosis, the actual median time to diagnosis was 4.5 months.[9] It has been estimated that every 4 weeks between scans represents the potential for a 13% progression.[25] Kasymjanova et al describe 2 studies and a meta-analysis demonstrating that increased wait times impart a negative effect on recurrence and survival.[23] In their own study, it was noted that reduced wait times particularly benefited Stage III NSCLC survival.[23]

Because pulmonologists may be the first specialist a patient sees, they are relied upon to diagnose, stage, and coordinate care for many patients with lung cancer.[26] Because Stage III NSCLC is a curative intent setting,[13,27] it is of particular importance to coordinate more complicated surgical, radiation, and chemotherapy care for these patients as soon as the diagnosis and stage have been ascertained.[7] While initial chest computed tomography or positron emission tomography (PET) scans often determine tumor size(s) and location(s), and presence of hilar or mediastinal nodes and extrathoracic lesions (excluding the brain), these studies cannot be the sole factors used in staging, and they falsely overstage 19% of the time and understage 13% of the time.[28] The ACCP guidelines recommend magnetic resonance imaging (MRI) of the brain for patients with clinical Stage III or IV disease with or without symptoms of intracranial disease,[29] whereas NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommend staging brain MRI in patients with clinical Stage IB (optional), IIA/B, IIIA/B/C and IV.[30]

Diagnostic procedures to obtain accurate histological diagnosis and staging and adequate tissue samples for molecular testing must be considered, ideally with input from a multidisciplinary team (MDT) composed of pulmonologists, thoracic surgeons, and radiology specialists who are board certified and have expertise in thoracic oncology whenever any stage of NSCLC is suspected.[30] PET imaging can be used to identify the optimal biopsy site that produces the highest yield, is minimally invasive, and is most likely to confer the highest staging.[30] Whenever possible, procedures should be combined (bronchoscopy and endobronchial ultrasound with needle aspiration of lymph nodes) to improve time to diagnosis and clinical staging.[30] Invasive mediastinal staging is recommended before surgical resection.[30] The organization of lung cancer care requires development of a multidisciplinary program committed but not limited to the expeditious coordination of the patient's care among various disciplines to avoid unnecessary tests and procedures, delay in care, costly care, and patient frustration and anxiety.[31] Multidisciplinary care has been shown to decrease time to diagnosis and improve referral for appropriate treatment.[32] In particular, patients with Stage III NSCLC are more

TABLE 1. Summary of NSCLC Staging & Prognosis[3,21,22]

Stage	TNM Classification[21] (Tumor, Node, Metastases)	Nodal Zones & Stations[3,22]		Treatment/Goal[22]	5-Year Survival[21]
IA_1	T1a or T1a(mi), N0, M0			Surgery or radiation	92%
IA_2	T1b, N0, M0			Surgery ± radiation, OR Radiation	83%
IA_3	T1c, N0, M0				77%
IB	T2a, N0, M0			Surgery ± Chemotherapy± Radiation	68%
IIA	T2b, N0, M0				60%
IIB	T1a-c, N1, M0 <or> T2a-b, N1, M0 <or> T3, N0, M0	N1 generally resectable N2 heterogenous resectability	N1 = Hilar Zone if ipsilateral • Station 10 (Hilar nodes) Peripheral Zone if ipsilateral • Station 11 (Interlobar nodes) • Station 12 (Lobar Nodes) • Station 13 (Segmental Nodes) • Station 14 (Subsegmental Nodes		53%
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or> T3-4, N1, M0 <or> T4, N1, M0			Surgery ± Chemotherapy ± Radiation	36%
IIIB	T3, N2, M0 <or> T4, N2, M0		N2 = Lower Zone if ipsilateral • Station 8 (Paraesophageal nodes) • Station 9 (Pulmonary ligament nodes) Subcarinal Zone if ipsilateral • Station 7 (Subcarinal nodes) Aortopulmonary Zone • Station 5 (subaortic & aortopulmonary nodes) • Station 6 (para-aortic nodes) Superior Mediastinal Zone • Station 2 (Upper paratracheal nodes) • Station 3 (Prevascular & retrotracheal nodes) • Station 4 (Lower paratracheal nodes)		26%
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or>	N2 = heterogenous resectability N3 generally non-resectable		Radiation ± Chemotherapy ± Immunotherapy	36-41%†
IIIB	T1a-c, N3, M0 <or> T2a-b, N3, M0 <or> T3, N2, M0 <or> T4, N2, M0		N3 = Supraclavicular Zone • Station 1 (Low cervical, supraclavicular, sternal notch nodes • contralateral mediastinal, contralateral hilar, ipsilateral/contralateral scalene, superclavicular nodes	Radiation ± Chemotherapy ± Immunotherapy	24-26%†
IIIC	T3-4, N3, M0				12-13%†
IVA	Any T, Any N, M1a-b			Palliative Care with Systemic Therapy	0%
IVB	Any T, Any N, M1c				0%

Abbreviations: M1a, separate tumor contralateral lobe or primary tumor with pleural/pericardial nodules or malignant effusions; M1b, single extrathoracic mass; M1c, multiple extrathoracic masses; mi, minimally invasive adenocarcinoma.
T1a ≤ 1cm; T1b >1cm, ≤ 2cm; T1c >2cm, ≤ 3cm; T2a >3cm, ≤ 3cm; T2b >4cm, ≤ 5cm; T3 >5cm, ≤ 7cm; T4 >7cm.
†Reflects changes in 5-year survival of all stage III NSCLC when staging included pathology information.

likely to receive appropriate treatment when referred to oncology specialists.[7] Still, data suggest that up to 20% of patients diagnosed with Stage III NSCLC are never evaluated by an oncologist.[33]

The tumor, node, metastasis (TNM) system for staging has been used since 1944.[8] Now governed by the International Association for the Study of Lung Cancer (IASLC), the eighth edition took effect in 2017.[21] Several changes from the seventh edition, including new TNM definitions and addition of categories, have caused shifts in staging, with a greater emphasis on tumor size and invasion of surrounding tissues.[3] As a result, Stage III now includes subtype C (T3-T4, N3, M0), which is still treated in a curative intent setting.[21] Additionally, nodal zones were further broken down into more specific stations that clearly define anatomic landmarks within each zone, as this too proved to be associated with prognosis.[3] Differentiating Stage IIIC from Stage IVA has provided more patients the opportunity to be treated in a curative intent setting, as further data collection and new research are expanding within each subtype and allowing for individualized treatment approaches.[3,21]

Clinically, the distinction between resectable and unresectable Stage III disease is of significance because unresectable Stage III does not afford a treatment path as well-established as resectable disease (surgery).[34] Unresectable generally includes Stage IIIA tumors (T1-T2 tumors with multiple positive ipsilateral mediastinal notes), often described as bulky or extensive; Stage IIIB (T1-T2 tumors with positive contralateral mediastinal or supraclavicular nodes or T3-T4 tumors with positive ipsilateral mediastinal nodes); and Stage IIIC (T3-T4 tumors with positive contralateral mediastinal or supraclavicular nodes).[11]

Treatment of Stage III NSCLC

Patients clinically determined to have resectable Stage III NSCLC are candidates for a variety of treatment options, none of which have proven to be superior.[11] The 2019 NCCN Guidelines® suggest the following course for resectable Stage III NSCLC: (1) Preoperative chemotherapy (CT) and radiation (CTR), or preoperative CT followed by postoperative RT (split-panel decision); and (2) surgery, using minimally invasive techniques where possible.[30] The panel acknowledges that controversy remains regarding the sequencing of surgery, chemotherapy, and radiation techniques.

The majority of patients with Stage III NSCLC have unresectable disease.[35] Platinum-based CT has been preferred over other chemotherapeutic modalities for over 3 decades.[36] Evidence supports its use as part of definitive CRT along with a minimum of 60 Gy in escalated doses; concurrent treatment is currently preferred over sequential in all histological findings.[30] Accelerated RT alone imparts some benefit to those who refuse CT.[11]

Severe immune-mediated adverse reactions are associated with all immune checkpoint inhibitors, including pneumonitis, causing discontinuation.[37] A recent retrospective single-center study suggests that patients who are on corticosteroids for cancer-unrelated indications have similar outcomes on immunotherapy as patients who are receiving 0 to < 10 mg of prednisone.[37] However, additional mechanistic studies as well as prospective clinical trials are needed to identify whether the use of corticosteroids affects specific aspects of the immune system necessary for immunotherapy activity. Optimal treatment duration for immune checkpoint inhibitors requires further study, and their use in patients with autoimmune disorders and a past organ transplantation should be avoided.[38]

Conclusion

Locally advanced and metastatic NSCLC patients have benefitted from intensive research into immunologic approaches to treatment. Accurate diagnosis and staging are critical, particularly in the differentiation between Stage III, which is treated with curative intent, and Stage IV, which is metastatic. CRT is the current standard of care for unresectable Stage III disease and has shown improvement in overall survival, while the introduction of immunotherapy following CRT treatment can be discussed as a treatment option. To reap the benefits of these advances in treatment, patients with suspected or confirmed lung cancer should be managed by an MDT that includes a pulmonologist, thoracic surgeon, and medical and radiation oncologists, and referral for appropriate treatment of Stage III and IV NSCLC is crucial to improving patient outcomes.

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