Multidisciplinary Management of Resectable Early-Stage Non–Small Cell Lung Cancer

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Presenters' disclosures of conflicts of interest are found at the end of this article.

https://doi.org/10.6004/jadpro.2022.13.3.25

Abstract

During JADPRO Live Virtual 2021, three advanced practitioners—in surgery, radiation oncology, and medical oncology—discussed their collaboration in the management of resectable early-stage non–small cell lung cancer. The presenters discussed the role of screening and early surgical resection, cancer surveillance after resection, adjuvant and neoadjuvant therapies, as well as novel therapies and their associated toxicities.

In 2021, approximately 235,760 Americans were diagnosed with lung cancer, which remains the leading cause of cancer-related deaths in the United States. In fact, last year, more than three times as many Americans lost their lives to lung cancer (155,870) than colorectal cancer (50,260), which is the second-leading cause of cancer death.

During JADPRO Live Virtual 2021, Jennifer Jacky, MSN, ARNP, AOCNP®, of Seattle Cancer Care Alliance, Kristin DeGroot, PA-C, of the University of Washington Medical Center, and Rebecca Denney, PA-C, of the University of Washington Medical Center, discussed the role of screening and early surgical resection of non–small cell lung cancer (NSCLC) and explained the role of adjuvant chemotherapy and chemoradiation. The presenters also discussed adverse events associated with recently approved and emerging systemic therapies in early-stage NSCLC.

As Ms. Jacky reported, despite significant advancements in therapeutics, lung cancer remains highly lethal. The 5-year survival rate of lung cancer that presents locally is 57%, but when it presents in the metastatic setting, the 5-year survival rate drops to 5%. When lung cancer is detected early, however, outcomes are significantly improved.

Although nearly 18% of men and women diagnosed with lung cancer are never-smokers, the major risk factor remains tobacco, and the risk of developing NSCLC increases propor-

J Adv Pract Oncol 2022;13(3):306–310

tionally with the number of cigarettes smoked. At the same time, said Ms. Jacky, the risk of developing NSCLC decreases with smoking cessation and approaches (but does not reach) that of non-smokers.

LUNG CANCER SCREENING

As Ms. DeGroot explained, increased screening over the past decade has been a major development in the treatment of lung cancer. In 2011, a national lung screening trial of 53,000 current or former heavy smokers showed that low-dose CT scan is the best method to detect cancer, significantly outperforming chest x-ray (24.2% vs. 6.9%, respectively). The study also showed that lung cancer screening can reduce the relative risk of dying from lung cancer by 20% and all-cause mortality by 7%.

According to Ms. DeGroot, the risks of lung cancer screening involve radiation exposure and cost, which is why low-dose CT scans are preferred to regular CT scans. There is also the risk of false-positive and false-negative results.

Although adopted by most expert groups, Ms. DeGroot, noted that uptake of lung cancer screening has been limited thus far to only 3% of eligible patients.

When lung cancer screening reveals a lung nodule, providers employ a set of guidelines called Lung-RADS (lung imaging reporting and data system). Patients are reviewed by a nodule board, which is a multidisciplinary team that includes radiologists, pulmonologists, and thoracic surgeons. The nodule board analyzes the patient's history, risk factors, and CT scans before making further recommendations, which may include surveillance, further testing, or referral to another specialty.

Most non-solid lung nodules are not lung cancer, said Ms. DeGroot, but are usually benign etiology that resolves over time. Further workup may require a dedicated chest CT scan and a PET scan (for staging purposes). Tissue diagnosis is more common for later stage disease.

Once the workup is complete, patients are reviewed by a thoracic tumor board, a multidisciplinary group that involves radiologists, pathologists, thoracic surgeons, thoracic medical oncologists, thoracic radiation oncologists, pulmonologists, and sometimes advanced practitioners (APs), although AP involvement varies from institution to institution. The thoracic tumor board discusses patient cases to determine the best approach to management of early-stage to advanced-stage lung cancer.

SURGERY: BEST CHANCE FOR CURE

According to Ms. DeGroot, surgery remains the best chance for cure for early-stage lung cancers and involves a thoracic surgeon. Important factors to consider before surgical resection are tumor stage and tumor location, which requires imaging review and mediastinoscopy or endobronchial ul-

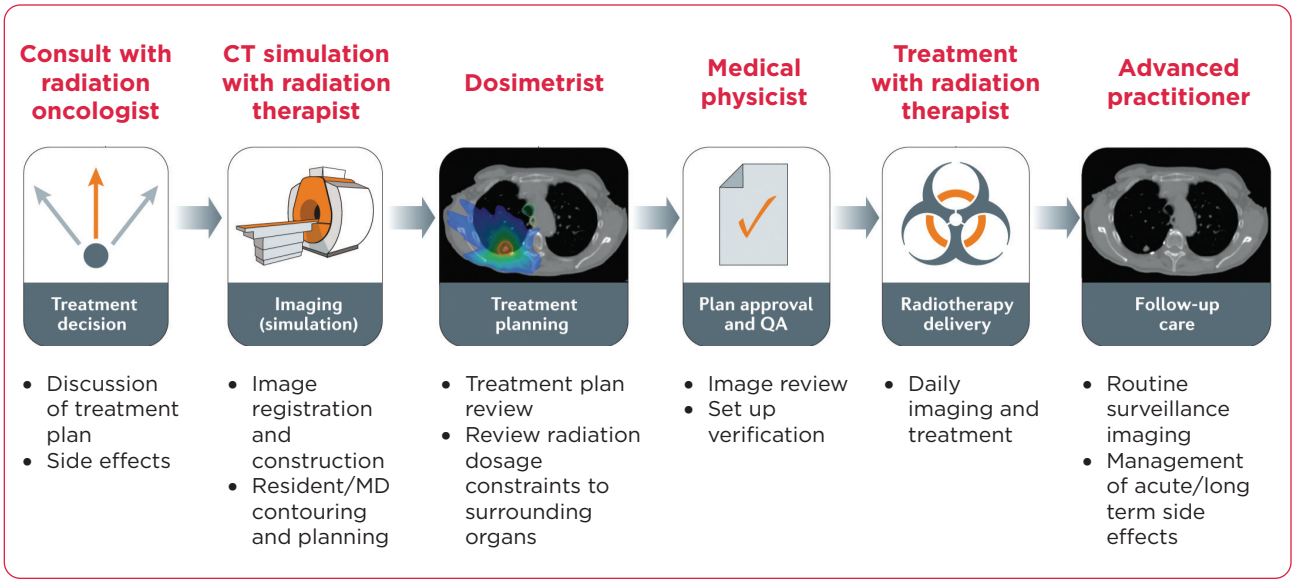

Figure 1. Patient treatment pathway. Adapted from Huynh et al. (2020).

trasound (EBUS) with biopsy depending on clinical stage. Mediastinoscopy/EBUS are optional for stage I disease if there is no evidence of mediastinal involvement on imaging, if the solid tumor is less than 1 centimeter, or if the non-solid tumor is less than 3 centimeters.

The functional status of the patient is another factor to consider, said Ms. DeGroot, who emphasized the importance of a detailed history. Additional testing may include pulmonary function testing and a cardiac evaluation such as echocardiogram. Alternatively, radiation therapy alone may be considered if the anesthesia risk is high or if lung function is poor.

Surgical approaches to lung cancer include video-assisted thoracoscopic surgery or VATS (this can be robotic assisted too) and open thoracotomy. The extent of resection can range from a wedge resection (just the tumor and surrounding tissue) to lobectomy to the entire right or left lung (pneumonectomy). As with any surgical procedure, said Ms. DeGroot, the risks are bleeding and infection.

Patients who undergo VATS surgery tend to stay in the hospital 2 fewer days than those who undergo a thoracotomy largely because of pain control. Oral pain medication is typically sufficient for VATS patients, said Ms. DeGroot, whereas thoracotomy patients require a thoracic epidural for pain control.

RADIATION

As Ms. Denney explained, radiation is also used to treat cancer and works in two different pathways: directly via DNA damage and cell death, and indirectly via free radicals that slowly cause cell death up to 8 weeks after radiation. Most radiation treatments are made using a linear accelerator or LINAC, which produces x-rays or photon beams. A radiation oncologist will collaborate with a radiation dosimetrist and medical physicist to develop a radiation treatment plan specific to each individual patient (Figure 1).

Types of radiation include the following:

- 3D conformal radiation: Manually set up

Table 1. Average Side-Effect Timeline for a 6-Week Course of Thoracic Radiation

		Treatment			Following completion			
		1 week	3 weeks	6 weeks	3 weeks	12 weeks	24 weeks	Lifetime risk
Acute	Fatigue	Start		Peak	Resolution			
	Radiation dermatitis		Start	Peak	Resolution			Lifelong sun precautions Hyperpigmentation
	Cough/ Shortness of breath		Start	Peak	Resolution			
	Esophagitis		Start	Peak	Resolution			
	Chest wall pain		Start	Peak	Resolution			< 1% risk of chest wall nerve damage
Long term	Radiation fibrosis					Start		Stabilizes over 1.5–2 years
	Pulmonary function loss					Start		On average, loss of 3%–10%
	Rib fracture						Start	Bone mineral density loss
	Cardiac toxicity							≤ 5% risk of cardiovascular disease 5–20 years
	Secondary malignancy							Age and other risk factor dependent

beam directions and adjust beam dose to achieve desired radiation plan.
- Intensity modulated radiation (IMRT): Uses an advanced computer program to calculate and deliver radiation. Allowing for more beams as well as shapes.
- Proton radiation: Uses proton beams instead of photons (x-rays). Beams stop after a certain distance and do not exit out the other side. Decreases amount of radiation dose to surrounding tissues such as the heart, lung, spinal cord, and esophagus.
- Stereotactic body radiation (SBRT): Often referred to as radiosurgery, SBRT is used in cases of nonresectable or high-risk surgical patients for the treatment of stage I lung cancer. Highly focalized with small margins, SBRT allows for very little effect to surrounding healthy tissues.

Locally advanced lung tumor regimens are cases involving the mediastinum with positive lymph nodes either seen on PET/CT or through biopsy confirmation with an endobronchial ultrasound and bronchoscopy. Treatment typically involves 6 weeks of daily radiation (approximately 60 Gy in 30 fractions) with weekly concurrent chemotherapy.

According to Ms. Denney, the side effects from radiation depend primarily on the location of treatment and the size of the radiation field. With SBRT, which is highly focalized in four to five treatments, for example, most patients experience minimal side effects (Table 1).

The long-term risks of radiation include scarring, loss of pulmonary function, bone loss, and cardiac toxicity, and secondary malignancy is a concern, depending on patient age. One side effect to watch out for is radiation pneumonitis, which is radiation-induced inflammation of the lung. As Ms. Denney explained, radiation pneumonitis is caused by an immune response to radiation and occurs in approximately 5% to 10% of the treatment population. It typically occurs 6 weeks to 6 months after radiation, and treatment is a long course of oral steroids.

Radiation is sometimes used in combination with immunotherapy with the goal of creating an immune-mediated response called an abscopal effect.

THERAPY FOR PATIENTS WITH RESECTED DISEASE

When patients have recovered from surgery or radiation, they then return to medical oncology, said Ms. Jacky, where APs work to help manage toxicities through treatment and respond to emergencies as they occur. Patients also may have a plan for neoadjuvant chemotherapy or chemotherapy concurrent with radiation or adjuvant chemotherapy. Targeted therapy with osimertinib (Tagrisso) and immunotherapy with durvalumab (Imfinzi) are additional options after surgery or chemoradiation.

"Chemotherapy for resected lung cancer is the standard of care for many patients," said Ms. Jacky. "It's believed that most relapses are distant from the surgical site and that micrometastatic disease was present at the time of surgery but not detected."

Because the benefit of adjuvant chemotherapy is greater for patients who have a higher risk of recurrence, Ms. Jacky underscored the importance of patient selection when choosing to administer these highly toxic therapies. In patients with stage I to IIIA completely resected NSCLC, adjuvant systemic therapy and adjuvant radiation therapy are associated with a 5% to 16% decrease in risk of recurrence or death at 5 years.

Histology also matters when choosing the type of chemotherapy to administer, said Ms. Jacky, but cisplatin is the standard-of-care base therapy.

Common side effects associated with adjuvant chemotherapy include kidney damage, fever/sepsis, nausea, hair loss, fatigue, neuropathy, and hearing loss.

TARGETED THERAPY

In advanced NSCLC, there are 11 targetable mutations, which are predominantly found in nonsmokers. Mutations of epidermal growth factor receptor (*EGFR*) are found on the surface of epithelial cells and are the most common targetable mutation (50% in Asians, 10% in Caucasians).

Osimertinib is an oral, third-generation EGFR tyrosine kinase inhibitor (TKI) that selectively inhibits both EGFR-TKI-sensitizing and *EGFR* T790M resistance mutations (Soria et al., 2018). Results of the ADAURA trial in patients with stage II to IIIA disease showed a disease-free survival

rate of 90% at 24 months vs. 44% with placebo (Wu et al., 2020). The side effects associated with osimertinib are mostly mild, including diarrhea, paronychia, dry skin, mouth sores, and the rare risk of interstitial lung disease and cardiac toxicity, said Ms. Jacky.

IMMUNOTHERAPY

Immunotherapy has become standard of care for metastatic NSCLC, but there is also an indication in patients who have received chemoradiation with complicated stage IIIA, bulky disease. Results of the phase III PACIFIC trial, which randomized patients with stage III NSCLC who did not have disease progression after 2 or more cycles of platinum-based chemoradiation to receive the immune checkpoint inhibitor durvalumab vs. placebo, showed increased survival at 2 and 3 years (Antonia et al., 2017).

Pneumonitis was the most common adverse event, but there are other immunotherapy-related toxicities to consider. According to Ms. Jacky, immunotherapy side effects are higher in patients with preexisting immune-mediated illness and are life threatening in less than 10% of patients. Steroids are often used to manage these effects, said Ms. Jacky, who noted that discontinuation of treatment depends on the grade and type of toxicity.

Following lung cancer treatment, CT surveillance is recommended every 3 to 6 months for 3 years and then every 6 months for 2 years. PET/CT or brain MRI are not routinely needed, said Ms. Jacky.

Disclosure

The presenters had no conflicts of interest to disclose.

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