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Considerations for the Surgical Management of Early Stage Lung Cancer During the COVID-19 Pandemic

Robert E. Merritt, Peter J. Kneuertz

Abstract

The highly transmissible novel coronavirus (COVID-19) has infected over 8.8 million people globally and has upended the delivery of health care in the United States, creating unprecedented challenges to providing care to patients with early stage non–small cell lung cancer (NSCLC). The initial surge of patients with COVID-19 that have flooded hospitals has put a strain on physical space, workforce, and supplies. In addition, social distancing and the risk of COVID-19 transmission has created significant barriers for thoracic surgeons to diagnose and treat patients. Many hospitals across the country have temporarily suspended elective operations to preserve hospital beds, ventilators, and personal protective equipment. Currently, the pandemic has greatly disrupted the current standard of resection after adequate staging with imaging and/or surgical staging for early stage NSCLC well beyond the initial acute phase; therefore, a new paradigm for effective management will need to be devised until the COVID-19 pandemic is eradicated with systematic vaccination and herd immunity. Thoracic surgeons will need to recalibrate their approach to ensure that patients receive timely and effective treatment for early stage NSCLC. The management of early stage NSCLC during the COVID-19 pandemic should be balanced with available hospital resources, risk of progression of disease, risk of transmission of COVID-19 to patient and surgeon, and the availability of alternative therapies. This article will address the current challenges with treating early stage NSCLC during the COVID-19 pandemic and provide a clinical framework for providing effective surgical therapy while mitigating the risk of transmission of the SARS-CoV-2 virus to patients and surgeons.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is responsible for coronavirus disease-2019 (COVID-19), which has resulted in the over 8.8 million infections and 460,000 deaths globally.¹ The SARS-CoV-2 is a novel coronavirus that was identified in December 2019 in Wuhan, China. The SARS-CoV-2 virus is highly contagious through human-human transmission. The reproductive ratio (R_0) for SARS-CoV-2 has been defined with an average number of 1.4 to 2.5 additional transmissions by any 1

initial infection, which can result in an exponential increase in infections.² Patients often develop fever, fatigue, myalgia, cough, and shortness of breath after transmission of COVID-19. Older patients or patients with preexisting medical conditions may develop viral pneumonia and progress to SARS and death. The incubation period for COVID-19 is ≤ 14 days (median, 5 days). The transmission mechanism of SARS-CoV-2 is primarily by respiratory droplets and direct contact.³ Aerosolized droplets of SARS-CoV-2 can be generated during endotracheal intubation, bronchoscopy, upper endoscopy, surgery involving the upper aero-digestive tract, and surgery involving the bronchus and lung. There is currently no evidence of airborne transmission of COVID-19 through aerosols of SARS-CoV-2; however, the Centers for Disease Control does currently recommend the use of N-95 respirator masks for aerosol-generating procedures for patients with confirmed COVID-19.

The current risk of transmission of COVID-19 from asymptomatic patients or minimally symptomatic patients to health care providers is currently unknown. The current proportion of

Thoracic Surgery Division, The Ohio State University Wexner Medical Center, Columbus, OH

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Address for correspondence: Robert E. Merritt, MD, Division of Thoracic Surgery, The Ohio State University Wexner Medical Center, Doan Hall N847, 410 W 10th Ave, Columbus, OH 43210
E-mail contact: Robert.Merritt@osumc.edu

asymptomatic patients with COVID-19 may be higher than previously expected, and current report suggested a range of 30% to 60%.⁴ The asymptomatic “super spreader” patient with COVID-19 poses the greatest risk of nosocomial transmission in the operating room. Using standard precautions in the operating room may not be the optimal protection during aerosol-generating procedures, which include bronchoscopy and lung resections. Standard precautions include droplet mask with eye protection. The aerosolized SARS-CoV-2 viral particles may be as small as 5 microns, which can be more effectively filtered by N-95 respirator masks. There is published data out of Hong Kong that reported no evidence of nosocomial transmission with appropriate personal protective equipment (PPE) early in the outbreak. However, there were reported health care worker COVID-19 transmissions in China prior to appropriate PPE utilization. Because SARS-CoV-2 was widespread in the Northern Italian population at time of patient zero presentation, it is difficult to discern nosocomial acquisition versus community acquisition.

In addition to the risk of nosocomial transmission of SARS-CoV-2, the COVID-19 pandemic has upended the normal delivery of health care in the United States and had temporarily resulted in the postponement of elective surgery for early stage non—small-cell lung cancer (NSCLC) across the country. The prolonged delay of lung cancer resections can result in progression of disease. In addition, social distancing policies have limited the ability of patients to be evaluated in outpatient clinics for their initial evaluation for NSCLC. Depending on the volume of COVID-19 cases in a given community, the surgical management of NSCLC can prevail with modifications to the standard practices. This article will provide a framework and practical guidance for modifying current practices for the management of early stage NSCLC that will ensure the safety of patients and thoracic surgeons and the timely treatment for early stage NSCLC during the ongoing pandemic.

Discussion

Preoperative Evaluation for Early Stage NSCLC

The standard evaluation for early stage NSCLC includes imaging studies, biopsy, and perioperative evaluation for surgery. Staging with computed tomography (CT) and positron emission tomography (PET) is acceptable evaluation of nodal metastasis or distant metastatic disease. Bronchoscopy and endobronchial ultrasound (EBUS) should be reserved for cases in which mediastinal lymph node metastasis are suspected owing to enlarged lymph nodes (greater than 1 cm) or hypermetabolic fluorine-18 fluorodeoxyglucose uptake. The SARS-CoV-2 virus enters the host through the upper airway and can become aerosolized during bronchoscopy. Recent experimental studies of the SARS-CoV-2 virus has demonstrated prolonged presence of aerosols of SARS-CoV-2 in the air for up to 3 hours.⁵

Practice Tip. Given the risk of nosocomial transmission of COVID-19 during aerosol-generating procedures, bronchoscopy should be minimized and are best performed at the time of resection. Cervical mediastinoscopy may be utilized as an alternative modality to EBUS for surgical staging of the mediastinum to avoid

bronchoscopy in patients with unknown or suspected COVID-19 status.

The assessment of pulmonary function is critical prior to surgical resection of early stage lung cancer. Standard pulmonary function testing with spirometry and diffusion capacity (DLCO) is the most common evaluation of pulmonary reserve prior to lung resection. The forced expiratory volume in 1 second (FEV-1) and DLCO are routinely measured during pulmonary function testing. During the COVID-19 pandemic, many pulmonary labs have been closed to minimize the risk of SARS-CoV-2 transmission, or test are delayed owing to pre-procedural testing requirements. Therefore, this important assessment tool for preoperative pulmonary function has become less accessible.

Practice Tip. Alternative assessment of tools for pulmonary function may be utilized to gauge pulmonary reserve during the initial surgical evaluation and determining suitability for resection. More in-depth assessment of functional level and direct observation of patient’s walking up flights of stairs are potential alternatives. The ability to climb 2 flights of stairs without desaturation on pulse oxymetry is a good indicator the patient may tolerate lobectomy. In addition, patients can perform the 6-minute walk test and record pulse oximetry values, which has shown good correlation with FEV1 and DLCO in patients with chronic obstructive lung disease.^{6,7}

To further minimize transmission of SARS-CoV-2, patients can be evaluated through virtual appointments with video consultations. In person, face-to-face patient encounters should be utilized in a limited fashion during the COVID-19 pandemic to adhere to the principles of social distancing and minimizing the risk of exposure to SARS-CoV-2. Although tele-health communication is preferred in the perioperative period to avoid bringing patients to the hospital and clinic facilities, it does also bear additional challenges for guiding patients during a stressful time after first receiving a cancer diagnosis, and the anxiety associated with having major lung cancer surgery. In addition, lung cancer surgery-related symptoms such as breathlessness and cough may be a source of additional social and psychological stress, as they may be associated with symptoms related to COVID-19 in the public eye.

Practice Tip. Attention to the social support system of the patient is especially important when communicating with patients virtually in the perioperative period. It may be helpful to encourage patients to involve close family members and/or friends to join the virtual clinic visits. Addressing the stigma associated with COVID-19 is key for patients who are likely to experience respiratory symptoms perioperatively.

Elderly patients and those with medical comorbid conditions are especially vulnerable to COVID-19 and are at higher risk for mortality. The relative risk of surgery as compared with nonsurgical treatment strategies for early stage NSCLC (ie, radiotherapy) is particularly important for these high-risk individuals and will depend on the specific conditions for the treating institutions. In general, although surgery may have a higher physiologic impact on the lung function in the early perioperative period, the time in the hospital may be reduced to a single short hospital stay as opposed to multiple trips to the hospital for nonsurgical treatments. Hence,

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Table 1 COVID-19 Screening Questionnaire

Call 48 Hours Prior to Surgery	Yes	No
Screening Questionnaire		
1. Any of the following symptoms (if acute onset):		
1. Fever (>100°F) regardless of onset		
2. Cough		
3. Shortness of breath		
4. Muscle aches (myalgia)		
5. Any other concerning or new symptoms?		
2. Have you been diagnosed with or suspected to have COVID-19 in the past 30 days?		
3. Have you been in close contact to a person who is suspected or known to be positive for COVID-19 in the past 30 days (ie, last seen that person ≤ 30 days ago)?		
4. Have you travelled to high-risk area in the last 30 days (ie, has been in that area last time ≤ 30 days ago) defined as “warning level 3” by the Centers of Disease Control and Prevention (CDC) per this weblink? https://wwwnc.cdc.gov/travel/notices		
Screen positive	Any yes	

Abbreviation: COVID-19 = coronavirus 2019

perioperative risk of COVID-19 infection assessment should entail a careful consideration of comorbid conditions and age, the extent of surgery, the surgical approach, and the expected postoperative course.

Practice Tip. Routine pre- and postoperative quarantining while maintaining a high activity level is advisable for all patients undergoing lung cancer surgery during the COVID-19 pandemic, and is especially important for patients of advanced age and with underlying comorbid conditions.

Triage for Surgical Resection of Early Stage NSCLC

The rapid surge of COVID-19 cases has placed a significant strain on hospital beds, ventilators, and PPE across the United States. As result, elective operative cases have been significantly limited or completely postponed depending on the regional incidence of COVID-19. The timely scheduling of lung cancer resections has been challenging given the limited operating room capacity during the COVID-19 pandemic. Surgical resection with a lymph node dissection is still the gold standard for the management of early stage NSCLC and should not be abandoned. The options for thoracic surgeons in these circumstances includes creating a case triage system for cases of early stage NSCLC in which patients can undergo timely surgical resection without increasing the risk for disease progression. The American College of Surgeons has provided thoughtful guidelines for the triage of cancer surgery during COVID-19, which were initially published in late March 2020, and which outline general principles for prioritization of surgical cases including thoracic malignancies during the acute phases of the pandemic; this has been updated to also include recommendations for the phases of recovery.⁸ The doubling time of lung cancer cells is between 45 and 200 days; however, the tumor volume can demonstrate exponential growth.⁶ An analysis of the United States

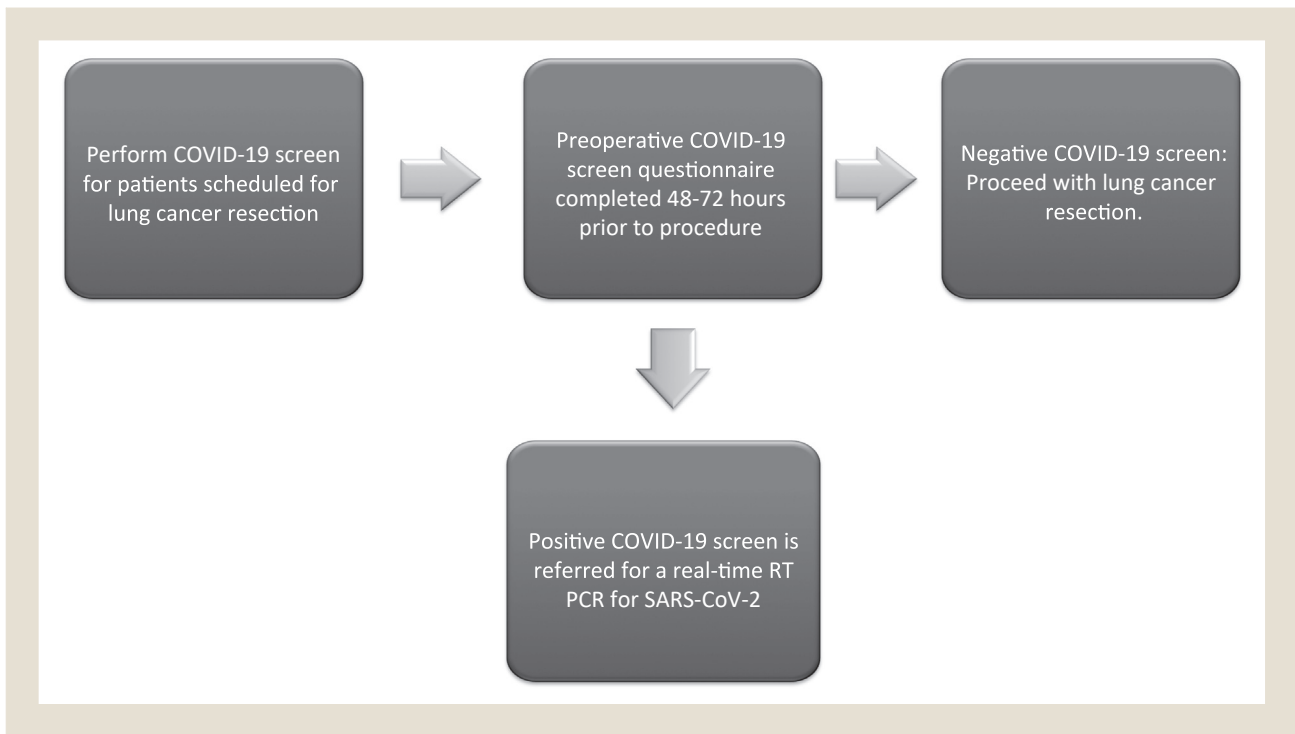
National Database demonstrated that a delay of over 8 weeks was an independent risk factor for disease progression for NSCLC.⁷ Therefore, prolonged delays greater than 2 months can result in disease progression in patients waiting to have surgery for early stage lung cancer. Surgery for early stage lung cancer therefore yields the highest priority categories for surgical cases according to the American College of Surgeons guidelines, specifically as a first priority case when survival is currently impacted by delay, or as a second priority case if survival may be impacted by a delay that exceeds 3 months.

From previous clinical experience, lung cancers have a spectrum of growth patterns and have different degrees of malignant potential based on their size, location, and degree of differentiation. In addition, a recent study has demonstrated that standardized uptake value (SUVmax) is associated with a higher rate of pathologic upstaging and more advanced disease at operation.⁹ The upstaging included more advanced tumor features, mediastinal nodal disease, pleural disease, and chest wall invasion. Although exact values defining high-risk behavior vary significantly between studies (ranging from 2.5 to 15), higher SUVmax has been repeatedly shown to pertain a worse prognosis.¹⁰

Practice Tip. SUVmax values obtained from PET/CT scans may provide a method for triaging early stage lung cancers in addition to histology and stage for prioritizing the more biologically aggressive tumors for immediate surgical resection.

The more indolent lung tumors, such as mixed ground glass tumors, can likely be postponed safely for a longer period of time without concern for disease progression. Surgical resection with a lymph node dissection remains the gold standard for management of early stage lung cancer; therefore, the authors recommend the proceeding with surgery whenever there is hospital capacity and resources are available to perform elective lung cancer surgery.

Figure 1 COVID-19 Perioperative Screening Schema



Abbreviations: COVID-19 = coronavirus 2019; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV2 = severe Acute respiratory syndrome coronavirus 2.

Preoperative Screening and Testing for SARS-CoV-2 Infection

Patients with COVID-19 typically present with fever, nonproductive cough, fatigue, and shortness of breath. Patients who are diagnosed with NSCLC often present with similar symptoms of COVID-19, which can be problematic for performing lung cancer resections. For this reason, preoperative screening for COVID-19 should be performed routinely prior to lung cancer surgery (Table 1). Nasal or nasopharyngeal swabs are utilized for obtaining specimens for testing.¹¹ The diagnosis of COVID-19 depends upon SARS-CoV-2 virus isolation and detection of viral nucleic acid. The full gene sequence of SARS-CoV-2 has been determined, and samples collected from the upper respiratory tract can be tested by real time reverse transcription polymerase chain reaction (RT-PCR) for diagnosis of COVID-19.¹² Patients who have a positive answer to any of the screening questions regarding COVID-19 symptoms or exposure to someone with COVID-19 should be referred for SARS-Cov-2 real-time RT-PCR testing prior to undergoing lung cancer surgery. Preoperative COVID-19 screening and testing should mitigate the risk of SARS-CoV-2 transmission from patients with unknown COVID-19. In addition, reports from China indicate that patients infected with SARS-CoV-2 in the perioperative period after thoracic surgical procedures have a high risk for death.¹³

Practice Tip. Based on these findings, detection of SARS-CoV-2 infection during preoperative testing should prompt postponement of the lung cancer surgery until the patient has fully recovered from COVID-19. Pulmonary resection impairs both lung function and

immunity, which can both contribute to poor prognosis for perioperative COVID-19. (Figure 1)

Intraoperative Safety Considerations for Lung Resection for NSCLC

The use of PPE is recommended by the Centers for Disease Control for every operative procedure for patients with a diagnosis of COVID-19 or suspected COVID-19.¹⁴ The conduct of pulmonary resections for early stage NSCLC involves surgical interruption of the bronchial mucosa and lung parenchyma. The SARS-CoV-2 virus enters hosts through the upper respiratory tract and can migrate to the lower respiratory tract. The surgical disruption of the bronchial mucosa and lung parenchyma can result in aerosolization of the SARS-CoV-2 virus, which can increase the risk of nosocomial transmission. N-95 respirator masks are recommended for use during aerosol-generating procedures on patients with COVID-19; however, N-95 respirator masks may be in short supply and are not recommended for use in patients without symptoms or low suspicion for COVID-19. For optimal protection for surgeons, anesthesiology staff, and operating staff, the authors recommend the use of N-95 respirator masks for bronchoscopy, EBUS, and all pulmonary resections (lobectomy, bi-lobectomy, pneumonectomy, and sublobar resections) regardless of the COVID-19 status. Preoperative testing for the SARS-CoV-2 virus does mitigate the risk for intraoperative transmission; however, the reported sensitivity for real-time RT-PCR SARS-CoV-2 test ranges from 30% to 60%.¹⁵ The accuracy of the real-time RT-PCR test is impacted by multiple factors, including sampling technique, sampling timing, and the quality of the testing reagents.

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Practice Tip. Based on the potential false negative results of the real-time RT-PCR SARS-CoV-2 test, the optimal PPE use strategy should include an N-95 respirator mask, which provides protection from aerosols of SARS-CoV-2 that can be generated during bronchoscopy and pulmonary resections for NSCLC. The personal protection of surgeons, anesthesia staff, and operating staff should be a high priority, and optimal PPE should be utilized for lung cancer resections.

Conclusion

The COVID-19 global pandemic has significantly disrupted the normal delivery of health care in the United States since the initial spike in reported cases in March 2020. The risk of nosocomial transmission of the SARS-CoV-2 virus coupled with the increase in hospital admissions of patients with COVID-19 has introduced ongoing challenges to the management of early stage NSCLC beyond the initial acute phase. Surgical resection remains the gold standard treatment for early stage NSCLC; therefore, modifications to this treatment strategy will have to be implemented during the COVID-19 pandemic to ensure timely surgical treatment that is safe for patients and health care providers. The utilization of telemedicine for the initial evaluation will minimize the risk of SARS-CoV-2 transmission. Routine PET/CT scans for staging will obviate the need for unnecessary surgical staging with EBUS, which is an aerosol-generating procedure that can result in airborne transmission of COVID-19. In addition, lung cancer resections should not be delayed for prolonged periods of time and should be triaged based on the clinical features of the tumor and SUVmax. Finally, universal testing for SARS-COV-2 with real time RT-PCR and optimal PPE with N-95 respirator masks should be utilized to mitigate the risk of nosocomial transmission of COVID-19 in the operating room during lung cancer resections.

Disclosure

The authors have stated that they have no conflicts of interest.

CRedit authorship contribution statement

Robert E. Merritt: Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Peter J. Kneuertz:**

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References

1. World Health Organization. Coronavirus disease 2019 (COVID-19 Situation Report). Available at: <https://www.who.int>. Accessed: April 12, 2020.
2. Phan LT, Nguyen TV, Luong QC, et al. Importation and human-human transmission of a novel coronavirus in Vietnam. *N Engl J Med* 2020; 382:872-4.
3. Jin YH, Cai L, Cheng ZS, et al. for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM). A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020; 7:4.
4. Qian G, Yang N, Ma AHY, et al. A COVID-19 transmission within a family cluster of presymptomatic infectors in China. *Clin Infect Dis* 2020 [epub ahead of print].
5. Van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med* 2020; 382:1564-7.
6. Agrawal MB, Awad NT. Correlation between six minute walk test and spirometry in chronic pulmonary disease. *J Clin Diagn Res* 2015; 9:OC01-4.
7. Fujimoto H, Asai K, Watanabe T, Kanazawa H, Hirata K. Association of six-minute walk distance (6MWD) with resting pulmonary function in patients with chronic obstructive pulmonary disease (COPD). *Osaka City Med J* 2011; 57:21-9.
8. American College of Surgeons. ACS guidelines for triage and management of elective cancer surgery cases during the acute and recovery phases of coronavirus disease 2019 (COVID-19). Available at: https://www.facs.org/-/media/files/covid19/acs_triage_and_management_elective_cancer_surgery_during_acute_and_recovery_phases.ashx. Accessed: June 21, 2020.
9. Verma S, Chan J, Chew C, Schultz C. PET-SUV max and upstaging of lung cancer. *Heart Lung Circ* 2019; 28:436-42.
10. Paesmans M, Berghmans T, Dusart M, et al. European Lung Cancer Working Party, and on behalf of the IASLC Lung Cancer Staging Project. Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. *J Thorac Oncol* 2010; 5:612-9.
11. Yu F, Du L, Ojcius DM, Pan C, Jiang S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. *Microbes Infect* 2020; 22:74-9.
12. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill* 2020; 25:2000045.
13. Li YK, Peng S, Li LQ, et al. Clinical transmission characteristics of Covid-19-A retrospective study of 25 cases from a single thoracic surgery department. *Curr Med Sci* 2020; 40:295-300.
14. United States Centers for Disease Control and Prevention. Interim infection and control recommendations for patients with suspected or confirmed coronavirus disease (COVID-19) in healthcare settings. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html>. Accessed: April 13, 2020.
15. Yang Y, Yang M, Shen C, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. *medRxiv* 2020. <https://doi.org/10.1101/2020.02.11.20021493>. Accessed July 20, 2020.