Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Surgery 168 (2020) 1–3

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

COVID-19 Pandemic

Is it ethically appropriate to continue surgical clinical trials during the COVID-19 pandemic?

The coronavirus disease 2019 (COVID-19) pandemic has greatly impacted both clinical care and its underlying ethical basis, shifting from the traditional patient-centered approach to a public health strategy.[1] As surgeons, we have been challenged to balance the risk of proceeding with planned operations with the concerns about the patient and about the health care system against the risk of delay. For the first time in the United States, we have found it necessary to consider the availability of appropriate hospital resources, the potential for increased adverse outcomes in occult COVID-19–positive patients, and limitations in preoperative testing, as well as potential health dangers posed not only to the patients but also to hospital staff, including the entire operating room staff—nurses, anesthesiologists, physicians, etc. At the University of Chicago (Chicago, IL), we introduced a scoring system to assist in the ethical triage of medically necessary, time-sensitive procedures, given that the imperative to halt all "elective" surgery does not adequately capture the nature of or define the types of nonemergency procedures that may still need to proceed.[2] We have found this approach to be particularly useful with respect to the constantly changing pressures on perioperative resources (anesthesiologists, nursing, personal protective equipment, blood, ventilators) and hospital inpatient capacity otherwise diverted to dedicated COVID units and intensive care units during various phases of the pandemic. The timing of surgery for cancer patients has been particularly thorny, and a number of groups have proposed thoughtful frameworks for these clinical decisions.[3–5]

So far unaddressed during this pandemic has been the status of surgical clinical trials. Specifically, is it ethically appropriate to continue enrollment and treatment of patients in clinical trials that include surgical intervention? If we continue such clinical trials, are we putting patients at greater risk of COVID-19–related complications? Could the pandemic inappropriately skew the results? If we expedite and prioritize surgical treatment for those patients who are part of a trial, are we unduly pressuring them to participate (a form of coercion)? In contrast, is it ethical to suspend future enrollment or active participation if it would potentially deny patients the benefit of novel therapeutic interventions or improved outcomes associated with the clinical trial? Although the ethical debates might apply across a broad range of clinical studies during the pandemic, we sought to focus specifically on surgical trials. We discuss here the ethics of clinical trial care within the surgical specialties and the pros and cons of participation in clinical trials during the COVID-19 pandemic, with a specific focus on surgical oncology and vascular surgery.

Surgical Oncology

The clinical trial portfolio is the core of any comprehensive cancer center. Oncologic therapeutic clinical trials offer patients access to exciting new treatments. These trials are designed typically to answer specific questions regarding treatment and outcomes and not the timing of surgical procedures or the frequency of visits and invasive procedures (at least not as primary objectives). The current need for social distancing and the limitations of health care resources has shifted priorities appropriately, but completely halting clinical trials would hinder dramatically the development of novel treatments and leave patients currently enrolled in these trials without access to potentially life-saving medications. The Cancer Therapy Evaluation Program at the National Cancer Institute (Frederick, MD) recognizes these issues and encourages sponsors, investigators, and institutional review boards to revise existing policies and procedures to mitigate risk and to protect trial participants while keeping clinical trials open. This program includes steps to alter the informed consent process, study visits and procedures, data collection, and the reporting of adverse events. For example, local treating physicians can perform a majority of study-related activities and administer all medications except investigational agents.[6]

The issues related to surgery in a clinical trial during the COVID-19 pandemic are more challenging. Many of the procedures typically cannot be performed by the surgeon at the local hospital, have strict time constraints dictated by inclusion/exclusion criteria in the trial protocol, and carry the potential to place an undue strain on limited inpatient resources and the health care workforce. Furthermore, cancer patients undergoing complex surgical procedures are inherently immunosuppressed and are at risk for superinfection by COVID-19 and the associated increase in morbidity and mortality. Therapeutic clinical trials that involve operative intervention tend to focus on locally advanced tumors and often involve induction therapies (chemotherapy, radiation therapy, or both) that increase the potential for postinduction fibrosis, which may increase the technical difficulty of an operative procedure and prolong the postoperative hospital stay because of perioperative complications. In the end, the decision to proceed with a planned cancer resection for a patient enrolled in a clinical trial is highly dependent on the institution's phase in the pandemic and availability of perioperative resources. The decision to proceed with an operation that is governed by strict time-dependent guidelines is often somewhat arbitrary and that time interval can likely be

https://doi.org/10.1016/j.surg.2020.04.024

prolonged without adversely affecting the surgical or oncologic outcomes. Although postponement of the operation may lead to a protocol violation by the predetermined principles of the clinical trial, in the current COVID-19 environment, such concerns should not impede appropriate safety-conscious, patient-centric, decision-making.

Although many institutions have adapted quickly to the ongoing crisis and have embraced the use of tele-health including video and telephone visits, such mechanisms may exclude patients from being considered for clinical trials. It is difficult ethically to impose additional preoperative testing for a clinical trial in a health care environment that is already burdened. Although several institutional review boards have responded to the crisis with modification of consents, this additional step poses substantial barriers to the expeditious conduct of multi-site clinical trials. In addition, several clinical trials that involve operative intervention depend on the processing of clinical specimens after a diagnostic and/or therapeutic procedure. The potential risk of viral transmission to health care workers from pathologic specimens places an undue burden especially with the additional processing required for a clinical trial.[7] Unique considerations also come into play for clinical trials involving neoadjuvant and adjuvant therapies that require the use of immunotherapy (including tumor-infiltrating lymphocyte, dendritic cell vaccines, and checkpoint inhibition). The delayed morbidity from the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) occurs because of a possible unknown host immune response, which is similar to autoimmune pneumonitis, a common side effect of immunotherapy. This possibility makes it virtually impossible to attribute the effects of the drug on patients who develop COVID-19 and creates conflict of therapy (autoimmune pneumonitis is treated with high-dose steroids, but COVID-19 acute respiratory distress syndrome is not). Several adjuvant trials rely on the use of maintenance chemotherapy for patients undergoing surgery. In the current context, the risks of additional immunosuppression with the risk of exposure to the patient and the health care team, make it difficult to continue such therapies. Finally, the additional risk of complications and death in patients undergoing operative intervention in known or occult COVID-19—positive patients can skew surgical outcomes. It is conceivable that stringent patient protections that are available during non-pandemic times are compromised. Small data series suggest that cancer patients in the postoperative period have an increased risk of contracting and dying from COVID-19.[8] The impact on the outcome is unknown, and this extreme circumstance could lead to type II errors in neoadjuvant and adjuvant studies and lead to loss of future therapeutic promise and financial investments. Similarly, the economic impact of this COVID-19 pandemic is still being estimated, but it is conceivable that small biopharmaceutical companies involved in drug development and trials might have to close their studies prematurely because of a loss of funding.

There are cities and hospitals where only urgent surgery is possible and others where resources still allow for high-priority, oncologic resections. At the University of Chicago, we have attempted to maintain patients already enrolled in clinical trials, but we have curtailed new enrollment dramatically because of the uncertainty of available resources and have focused our research efforts on COVID-centric issues. Only low-risk trials with novel agents and unique therapies remain open to enrollment, but, as expected, accrual has slowed tremendously. Trials that include surgery do not fall into this category. Surgical trials typically require multiple therapies on rigid time schedules and are deemed imprudent in our current environment. It is unclear how these decisions will impact cancer care for individual patients and the advancement of our science, but, in a time of limited resources, we do not want to embark on a treatment strategy that we cannot potentially safely complete. However, it is not lost on us that clinical cancer trials that do or do not involve surgery are invaluable in defining new treatment paradigms that lead to improved outcomes for cancer patients, and it is known that just by participating in a clinical trial, derivative benefits in patient outcomes are the rule. Therefore, striking the correct balance between these two conflicting concepts is the essence of the ethical dilemma we are facing.

Vascular Surgery

The majority of clinical trials in vascular surgery involve the use of medical devices or a surgical procedure to treat peripheral artery disease, carotid artery disease, or aortic aneurysms/dissections. At the University of Chicago, we participate in a number of such trials. Many of these large, multi-institutional device trials are sponsored by industry. In light of the COVID-19 pandemic, all vascular clinical trials have been halted. One of the large device trials that was scheduled to begin in March 2020 has been delayed during the COVID-19 pandemic because of the need to eliminate “elective” cases for the well-being of individual health care systems. The decision on the part of industry to suspend such clinical trials has been met largely with support from vascular surgeons.

What is the ethical basis for supporting this decision even though it means that some patients are not getting the latest and potentially more effective devices to treat their vascular disease? The care and focus of clinical trials in vascular surgery are both resource intensive and time sensitive. Using our current framework of medically necessary, time-sensitive procedure prioritization, we have focused attention on patient care issues related to critical limb ischemia, symptomatic carotid artery disease, and symptomatic or ruptured aortic aneurysms. As such, vascular surgeons should not utilize scarce operating room time or clinic time to investigate novel devices with unknown outcomes. It is our belief that this same prohibition on vascular clinical trials should also apply to devices (approved by the US Food and Drug Administration) that are being investigated under a registry designation. By halting the enrollment of patients into such trials, we relieve the pressure placed on surgeons to enroll patients in a clinical trial that could negatively impact the timely care of other patients whose needed procedures have greater medical urgency. Most important, we believe that in the present environment, surgeons should provide care that is the best known “standard of care” and that can provide the most benefit to our patients and minimize the impact on our hospital and health care systems with unknown outcomes from devices. Finally, patients should not feel pressured to participate in clinical trials in the hope that by enrolling they may be given an advantage to have surgery sooner.

Matters for Consideration

In conclusion, the COVID-19 pandemic has created both clinical and ethical dilemmas for surgeons. We believe that continuing surgical clinical trials at the present time poses unique ethical concerns. Before continuing to enroll patients in surgical trials, we believe that surgeons must carefully consider the type of trial, the institutional status with respect to scarce resources, and the potential risk/benefit ratio to patients and health care workers involved. We have decreased our clinical trial efforts markedly during the pandemic to minimize patient coercion and to maximize the use and availability of patient care resources for evidence-based procedures.

Funding/Support

The authors have no funding sources to report.

Conflict of interest/Disclosure

Dr. Milner is a consultant for Endospan, Medtronic and for WL Gore. The authors have no additional conflicts to report.

Ross Milner, MD*, Jessica Donington, MD, Jeffrey B. Matthews, MD, Mitchell Posner, MD, Kiran Turaga, MD, Peter Angelos, MD, PhD
Department of Surgery
The University of Chicago Medicine
Chicago, IL
* Reprint request
E-mail address: rmilner@surgery.bsd.uchicago.edu (R. Milner).

Accepted 20 April 2020

References

1. Angelos P. Surgeons, ethics, and COVID-19: early lessons learned [e-pub ahead of print]. J Am Coll Surg. 2020 Jun;230(6):1119-1120. https://doi.org/10.1016/j.jamcollsurg.2020.03.028. Epub 2020 Apr 10.
2. Prachand VN, Milner R, Angelos P, et al. Medically necessary, time-sensitive procedures: a scoring system to ethically and efficiently manage resource scarcity and provider risk during the COVID-19 pandemic [e-pub ahead of print]. J Am Coll Surg. 2020. https://doi.org/10.1016/j.jamcollsurg.2020.04.011.
3. Bartlett DL, Howe JR, Chang G, et al. Management of cancer surgery cases during the COVID-19 pandemic: considerations. *Ann Surg Oncol*. 2020;27:1717–1720.
4. Qadan M, Hong TS, Tanabe KK, Ryan DP, Lillemoe KD. A multidisciplinary team approach for triage of elective cancer surgery at the Massachusetts General Hospital during the novel coronavirus COVID-19 outbreak [e-pub ahead of print]. Ann Surg. 2020. https://doi.org/10.1097/SLA.0000000000003963.
5. Turaga K, Girotra S. Are we harming cancer patients by delaying their cancer surgery during the COVID-19 pandemic? Ann Surg. https://doi.org/10.1097/SLA.0000000000003967
6. McDermott MM, Newman AB. Preserving clinical trial integrity during the coronavirus pandemic [e-pub ahead of print]. JAMA. 2020. https://doi.org/10.1001/jama.2020.4689.
7. Iwen P, Stiles K, Pentella M. Safety considerations in the laboratory testing of specimens suspected or known to contain the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Lab Med*. 2020;51:239–242.
8. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21:335–337.