Cancer Treatment Delays Caused by the COVID-19 Pandemic May Not Hinder Outcomes

In response to the coronavirus disease 2019 (COVID-19) pandemic, health care providers and institutions have recommended delaying the treatment of some patients with cancer, especially during peaks of infection incidence, with the intent of reducing patient exposure to the virus and prioritizing health care resources. For patients and clinicians who may be uneasy about delaying cancer treatments during the COVID-19 pandemic, 2 new studies that analyzed data from the National Cancer Data Base (NCDB) have offered some reassurance. Both investigations—a breast cancer study published in the *Journal of the American College of Surgeons* (2020;231:434-447.e2. doi:10.1016/j.jamcol.surg.2020.06.021) and a prostate cancer study that appeared in *JAMA Oncology* (2020;6:1630-1632. doi:10.1001/jamaoncol.2020.3545)—concluded that, in many cases, delayed breast surgery and prostate radiotherapy after diagnosis will not lead to worse outcomes.

**Breast Cancer Study Details**

The breast cancer study focused on patients with ductal carcinoma in situ (DCIS) and early-stage, estrogen receptor–positive (ER+), invasive breast cancer. Prior to the pandemic, such patients typically received primary surgical treatment soon after diagnosis. According to lead author Christina A. Minami, MD, MS, a surgeon in the breast surgery division at the Dana-Farber/Brigham and Women’s Cancer Center at Milford Regional Medical Center in Boston, Massachusetts, researchers sought to determine if there were likely to be any negative impacts on pathology upstaging and overall survival as a result of the surgery delays.

To address this clinical question in a timely manner, Dr. Minami and her colleagues conducted a retrospective analysis of the NCDB, a clinical oncology database sourced from hospital registry data and jointly sponsored by the American College of Surgeons and the American Cancer Society (ACS). The database encompasses approximately 70% of new cancer diagnoses in the United States. “Given our study question, this was simply the most appropriate data set,” she says, because the NCDB includes disease-specific variables (such as clinical and pathologic stage) as well as treatment-specific variables (such as endocrine therapy) that are not as robustly captured in other cancer-specific data sets.

The researchers identified 378,839 records in the NCDB from patients with either DCIS or ER+, cT1-2N0 breast cancer who were treated from 2010 through 2016, noting each patient’s time from diagnosis to surgery. Of the 99,749 patients with DCIS included in the study, approximately 84% (83,754 patients) had ER+ disease and the remaining...
patients (15,995 patients) had ER-negative disease. According to Dr. Minami, although neoadjuvant endocrine therapy (NET) was recommended by the COVID-19 Pandemic Breast Cancer Consortium for patients with delays in surgical treatment, it is important to note that NET was not in wide use prior to the pandemic for patients in the United States with DCIS or early-stage, ER+ breast cancer.

Among the patients with cT1N0 disease, less than 1% (1591 patients) underwent NET, and the remaining patients underwent a primary surgery. Approximately 3.3% of patients with cT2N0 disease underwent NET (1880 patients). The researchers found there were too few patients with DCIS in the NCDB who underwent NET for reliable statistical analysis. Therefore, these patients were excluded from the study.

The researchers found that greater than 98% of all patients undergoing primary surgical procedures were operated on within 120 days. Among the patients with cT1-2N0 disease who were treated with NET, approximately 59.6% of patients with cT1N0 disease and 30.9% of patients with cT2N0 disease underwent surgery within 120 days. Investigators found that a longer wait for surgery was not associated with pathologic upstaging. However, they did discover that patients with ER+ DCIS had a slightly greater chance of pathologic upstaging when surgery was delayed for 60 to 120 days (odds ratio [OR], 1.15; 95% confidence interval [95% CI], 1.08-1.22) or more than 120 days (OR, 1.44; 95% CI, 1.24-1.68). They found that patients with ER-negative DCIS had a greater risk of upstaging when surgery was delayed for more than 120 days after diagnosis (OR, 1.36; 95% CI, 1.01-1.82), but that there was no excess risk of upstaging associated with shorter delays. Most important, this increase in upstaging among patients with DCIS had no impact on their overall survival, Dr. Minami adds.

“The findings of our study have been suggested by previous data, and certainly given what we know about DCIS and early-stage hormone receptor–positive breast cancer, we did not anticipate any changes in survival or meaningful pathologic upstaging from surgical delays due to COVID—hence the recommendations that were published by the COVID-19 Pandemic Breast Cancer Consortium,” she says. “However, we did not have any data that directly examined this question. Thus, while our findings are not particularly surprising, they do fill a gap in knowledge and have been useful in reassuring our patients.”

One important point about the study, according to Dr. Minami, is that although it used the best retrospective data currently available and forecast the possible outcomes of patients experiencing oncologic surgical postponements, “The determination of the actual impact of COVID-19–related surgical delays will require additional studies after the pandemic, meaning the true ramifications of these delays won’t be known for some time. Understanding the possible outcomes earlier, however, could be useful in effectively counseling and reassuring patients about surgical delays and the broadened use of NET.”

The report in the Journal of the American College of Surgeons acknowledged some unavoidable limitations. “We trust that researchers will recognize that our study used retrospective data, and thus the study population represents a very different population of patients who underwent surgical delays during the height of the pandemic,” says Dr. Minami. She also noted that during the prepanademic study period, patients who received NET may have been selected for this treatment because of factors such as older age and coexisting illnesses. “We would thus encourage researchers to rigorously follow the true outcomes of our cancer patients treated during the pandemic to understand how deviations in care truly affected their outcomes,” she says.

David J. Winchester, MD, an endowed chair of surgical oncology at NorthShore University HealthSystem and a clinical professor of surgery at the University of Chicago Pritzker School of Medicine in Evanston, Illinois, believes this is an important study that should help allay concerns regarding a backlog of breast cancer operations created by the COVID-19 pandemic. “This study helps to justify this approach and may help to support a similar strategy for a COVID resurgence or another unrelated global health catastrophe that disrupts cancer care delivery.”

Time to surgery, the independent variable researchers focused on in the study, had multiple explanations related to patient characteristics during 2010 through 2016, in contrast to being an imposed sanction created by a pandemic, Dr. Winchester notes. “However, by controlling other variables (patient age and race, Charlson Comorbidity Index score, insurance status, treatment facility type, tumor histology, operation type) and relying upon the [large] magnitude of the NCDB data, the biology should be similar,” he says. “The important conclusion from the data is straightforward—time to surgery greater than 120 days after diagnosis for ER-positive breast cancer does not change survival if neoadjuvant endocrine therapy is employed. That knowledge is the first step to endorse this
strategy. Convincing the patient is the second.”

**Prostate Cancer Study Details**

According to Vinayak Muralidhar, MD, MS, senior author of the *JAMA Oncology* study and a resident in the radiation oncology department at Dana-Farber Cancer Institute and Brigham and Women’s Hospital, the research that he and his colleagues conducted is relevant to care during the COVID-19 pandemic because it provides evidence supporting the lack of a decrement in overall survival if radiotherapy (RT) is delayed for patients with localized, unfavorable prostate cancer with an intermediate risk, high risk, or very high risk of recurrence (according to National Comprehensive Cancer Network criteria) who are receiving adjuvant or neoadjuvant androgen deprivation therapy (ADT). Dr. Muralidhar notes that 2 earlier studies were not powered for analyses of overall survival, and the patients included appeared to be younger and healthier than typically found for this disease. “Those 2 randomized controlled trials, which suggested no difference in overall survival based on the relative timing of radiation and ADT, were not designed as non-inferiority trials, necessitating further analysis of the potential effects of treatment delays,” he says.

Echoing a similar rationale for using the NCDB as that stated by the authors of the study published in the *Journal of the American College of Surgeons*, Dr. Muralidhar says he and his colleagues chose the database primarily because it has a large sample size, information that allows the relative timing of ADT and RT to be extrapolated, good follow-up data, and extensive clinical and sociodemographic data for which they were able to adjust “Furthermore, it is quite diverse in its geographic and sociodemographic extent, which can help the generalizability of our findings,” he says. “The NCDB is, of course, limited by its retrospective nature and possible errors in reporting of the data, which should nuance how one interprets findings using the NCBD.”

The researchers identified NCDB records from men who had been diagnosed with prostate cancer between 2004 and 2014 and who were treated meeting the National Comprehensive Cancer Network’s criteria for patients with unfavorable disease at intermediate risk of recurrence (19,258 patients) or high and/or very high risk of recurrence (44,600 patients), and who had been treated with external beam RT and ADT. The median follow-up was 6.3 years and 5.8 years, respectively, for the patients at intermediate risk and those at high and/or very high risk.

To approximate analyses from prior clinical trials, start times for RT and ADT were categorized as follows:

- **RT 0 to 60 days after the initiation of ADT**: 3572 patients.
- **RT 1 to 60 days after the initiation of ADT**: 23,207 patients.
- **RT 61 to 120 days after the initiation of ADT**: 52.4%.
- **RT 121 to 180 days after the initiation of ADT**: 58.9%.
- **RT 181 to 240 days after the initiation of ADT**: 54.8%.
- **RT 241 to 360 days after the initiation of ADT**: 58.9%.
- **RT 361 to 720 days after the initiation of ADT**: 58.9%.
- **RT 721 to 180 days after the initiation of ADT**: 58.9%.
- **RT 1 to 60 days after the initiation of ADT**: 51.7%.
- **RT 61 to 120 days after the initiation of ADT**: 62.3%.
- **RT 121 to 180 days after the initiation of ADT**: 58.9%.
- **RT 181 to 240 days after the initiation of ADT**: 58.9%.
- **RT 241 to 360 days after the initiation of ADT**: 58.9%.
- **RT 361 to 720 days after the initiation of ADT**: 58.9%.
- **RT 721 to 180 days after the initiation of ADT**: 58.9%.
- **RT 121 to 180 days after the initiation of ADT**: 58.9%.

Using multivariable Cox survival analyses adjusted for Gleason score, prostate-specific antigen level, T category, race, age, year of diagnosis, treatment facility type, geographic region, county type (rural or urban), distance traveled to the treatment facility, Charlson-Deyo Comorbidity Score, insurance status, and zip code–wide median household income, the researchers did not find overall survival differences between men in either of the recurrence risk categories who received later RT (up to 6 months after the initiation of ADT) and those with RT administered before the initiation of ADT.

Because the study was based on a large, diverse data set of patients in the United States who have localized prostate cancer and are receiving ADT, Dr. Muralidhar believes the takeaway message is that delaying RT for up to 6 months may not be associated with worse overall survival. “It should also help cancer researchers elucidate other cancers and clinical settings in which delays do not affect overall survival and, importantly, help identify situations in which delays in treatment
may be harmful,” he says. He and his colleagues believe clinicians and patients can use the study’s findings to make decisions regarding the timing of treatment, especially weighed against the risk of contracting COVID-19 in a hospital setting. “Each decision must, of course, be individualized, taking into consideration each patient’s own context and preference,” he adds. “We hope our findings provide reassurance to patients and providers as they make these important decisions about care.”

William K. Oh, MD, chief of the hematology and medical oncology division at the Icahn School of Medicine at Mount Sinai in New York City, says the study was a “timely look” at the potential consequences of delaying definitive RT in men with intermediate-risk and high-risk localized prostate cancer. “Given how COVID-19 has disrupted practice patterns in the US and around the world, the investigators found that even if RT was given much later than usual, no differences in survival at 10 years were seen. This will reassure patients that if they are concerned to come in for frequent radiation visits, they can potentially hold off on that component until the pandemic risks diminish.”

Dr. Oh, who also is the deputy director of the Tisch Cancer Institute and a professor of medicine and urology at the Icahn School of Medicine at Mount Sinai adds, “We know that COVID-19 has disrupted many aspects of routine cancer care. In terms of men who are diagnosed with localized but higher-risk prostate cancer (and thus are potentially curable), delaying treatment could have an impact on mortality. This study at least reassures us that ADT is a good temporizing measure for patients who cannot or will not start RT in the usual time frame.”

Durado Brooks, MD, MPH, vice president for cancer control interventions at the ACS in Atlanta, Georgia, reviewed both the breast and prostate cancer studies and says they simply reinforce the fact that delays, particularly relatively short delays of 1 or 2 months, in initiating treatment are not likely to have a major long-term impact on outcomes. “I think that’s reassuring—in particular for patients, but for clinicians as well,” he says. “We always worry that if we don’t do something immediately, the patient is going to suffer long-term repercussions, so it’s reassuring that both of these studies seem to indicate that short delays, particularly in the face of these kinds of external challenges, are probably not going to have a pronounced long-term impact, but it’s still going to be important that they address care of these patients as soon as it’s feasible, based on local situations and capacity.”

According to Dr. Brooks, one area on which the ACS is currently focused due to the COVID-19 pandemic is convincing clinicians and their patients to catch up on cancer screenings they may have postponed. “Once it became clear to us that the spread of COVID-19 was not occurring in a uniform fashion across the country, we modified our guidance and are developing tools for clinicians and patients to use,” he says.

The first tool is screening guidance entitled “Reigniting Colorectal Cancer Screening as Communities Face and Respond to the COVID-19 Pandemic: A Playbook” (https://nccrt.org/resource/a-playbook-for-reigniting-color-rectal-cancer-screening-as-communities-respond-to-the-covid-19-pandemic/). Released by the National Colorectal Cancer Roundtable and the Colorectal Cancer Alliance, the document is described as “an action-oriented playbook for how National Colorectal Cancer Roundtable members, 80% pledged partners, and colorectal cancer screening advocates across the nation can work together to reignite our screening efforts appropriately, safely, and equally for all communities.”

In addition, Dr. Brooks says that by press time, guidance covering screening for breast, cervical, and lung cancer will be available. “I would encourage primary care clinicians to look at these new ACS tools because they are the primary audience we developed them for,” he says.

doi: 10.3322/caac.21651