Treating COVID-19 Positive Cancer Patients with Radiation Therapy: Case Report From Epicenter of The Pandemic.

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Case report

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Abstract

Coronavirus -19 (Sars-cov-2 or Covid-19) pandemic has resulted in unprecedented clinical challenges across the globe. Outcomes of patients with this infection are likely dependent on underlying comorbidities that predicts worse outcome in older patients. However, it is unknown whether Covid-19 infected cancer patients receiving radiation therapy (RT) have any different outcome than non-infected patients. We present the first series of Covid-19 infected patients that received RT for malignancy, their outcome, and toxicities.

Introduction

The Covid-19 pandemic has resulted in unprecedented challenges globally, including social, healthcare, economic and cultural issues. It is caused by a virus called severe acute respiratory coronavirus-2 (SARS-COV-2) (1). The disease was initially seen in patients in December 2019 and subsequently spread to other parts of the world rapidly with reported mortality from all parts of the globe. The virus has been sequenced, and many groups worldwide are involved in studying the virus, the development of detection kits, the development of antibody tests, and vaccine development (2). A lot is unknown about the impact of Covid-19 infection on various health situations, such as cardiovascular diseases, diabetes, cancer, or other immunosuppressive conditions. However, there is strong evidence that mortality is higher in patients with comorbidities that get this infection (1). Regarding cancer patients that get infected with the Covid-19 virus, it is not clear whether the virus has any impact on cancer progression, tolerance to chemotherapy or radiation therapy (RT), and overall prognosis (3).

In this study, we document our experience from the epicenter of the pandemic in treating 5 Covid-19 positive patients with RT and data collected via our ONCORA data collection system that is integrated with our electronic medical records.

Case 1

A 76 y female with FIGO stage IIA cervical clear cell adenocarcinoma. Recommended chemoradiation therapy (CRT). Patient's past medical history of depression, bipolar disorder, hypertension, and Diabetes Mellitus a presented with abdominal pain and bloody urine. CT abdomen showed free air and a cervical/pelvis mass. Biopsy of the cervical mass showed clear cell adenocarcinoma. Work-up, including a PET-CT, showed a large cervical mass with no distant disease. The patient was diagnosed with FIGO stage IIA cervical cancer. RT consulted for vaginal bleeding and management of cervical cancer. Chemoradiation (CRT) was recommended. The patient started with CRT. Recommended RT dose 4500cGy in 180cGy/f for a bulky 10cm mass followed by brachytherapy. RT started February end 2020 as an inpatient. On treatment 17/25, the patient was showing signs of labored breathing, and O2 saturation was checked, which was 88% on 2 liters of O2 while lying flat. The patient was brought back to a high fowlers position, and O2 saturation increased to 96% on the 2L nasal cannula. Axillary temperature

obtained; Temperature was 101.6. RT was withheld, and the patient was tested for Covid-19, which was positive.

Treatment summary: Planned external beam with IMRT to 45 Gy /25 fractions followed by four HDR Tandem and Colpostat application sessions. However, the patient completed 21.6Gy in 12 fractions. She developed abdominal distension and possible perforation. She was admitted and developed pulmonary symptoms and died subsequently.

Case 2

A 70-year-old female with T3N2bM0 Stage IIIB unresectable squamous cell carcinoma of the vulva. In December 2019, the patient was noted to have a small vulvar bump that had increased in size since August 2019 and was becoming increasingly painful and uncomfortable. She described a large irregular multilobulated left labial mass with excoriation.

The physician noted minimal mobility of the patient due to obesity plus a fungating > 10cm vulvar mass. Biopsy of the vulvar mass showed squamous cell cancer (SCC) (December 2019).

Work-up including a CT Chest/abdomen/pelvis showed mildly enlarged left common iliac lymph node 1.0cm short axis and a markedly enlarged left inguinal lymph node that was 4cm. Past medical history was significant for IVC filter, status post cholecystectomy. PET-CT scan in January 2020 revealed a large elongated intensity hypermetabolic vulvar mass extending into the contiguous inferior perineum, consistent with vulvar cancer. 1 cm short-axis left common iliac lymph mode moderately activity, consistently with metastatic disease. A large 4 cm left inguinal lymph node, which is suspicious on CT, demonstrated no significant hypermetabolic activity.

The treatment team recommended CRT. 5-Fluorouracil/mitomycin C was planned, and the patient was not deemed a good candidate for cisplatin. RT was planned with IMRT with image guidance to the vulvar tumor, inguinal lymph nodes, and pelvis lymph nodes to a dose of 6400 cGy (to gross disease) in 2Gy/fraction over 61/2 weeks.

The patient started CRT in mid-March 2020. Treatment showed good response and resulted in tumor shrinkage but was associated with moist desquamation of the skin and diarrhea, which was treated with Calendula and Imodium, respectively. Treatment break was given at the end of March 2020 for five days for pain and blisters at the treatment site. The patient returned to treatment but in the second week of April 2020 when she was diagnosed with Covid-19 by PCR test since the patient's oxygen saturation decreased overnight and was on oxygen 2L via nasal cannula O2 saturation was 92% on 2 L oxygen. The patient's inpatient note was recorded as 'Patient admitted for hypoxemia secondary to COVID and supratherapeutic INR due to hypercoagulative state secondary to COVID and using Coumadin.' The patient was prescribed Plaquenil, and her symptoms improved.

Patient treatment was restarted. In summary, Planned external beam with IMRT to 64Gy /32 fractions. Patient completed 56Gy/28fractions. The patient's treatment interrupted due to poor nursing care at the

facility (possibly due to her Covid-19 diagnosis), and she decided to stop the treatment. She has a nearly complete clinical response and will be followed with clinical examination and follow-up imaging.

Case 3

A 36-year-old female with T1N0M0 Adrenocortical Carcinoma, s/p robotic-assisted laparoscopic right adrenalectomy in March 2020. Pathology showed Stage I, high-grade adrenocortical carcinoma, high mitotic count, and Ki-67 40-50%. The patient was recommended adjuvant radiotherapy to the right adrenal bed and was planned for a total dose of 45Gy in 1.8Gy/fraction using IMRT.

Treatment: right adrenal bed, 3/11/20-4/20/20, 4500cGy, 180cGy/f, IMRT. The patient tested positive for Covid-19 on 3/25/20 but was not hospitalized.

Summary: In August 2019, the patient evaluated for left flank pain, work up showed incidental finding of an adrenal mass. CT abdomen/pelvis showed an approximately 3 cm right adrenal mass. Left kidney ultrasound in august 2019 showed moderate left hydronephrosis due to a ureter stone. MRI abdomen September 2019 showed an indeterminate 3.5 cm right adrenal mass. Patient was evaluated by endocrinology that included work up such as 24 hour urine cortisol, 14 mcg/24h, ACTH- 1.7 pg/mL (Low), Cortisol AM- 3.0 (Low), Normetanephrine: 13 pg/mL, metanephrine - <10 pg/mL, Renin activity plasma- 0.581 (WNL). She had surgery in early January 2020, s/p robotic-assisted laparoscopic right total adrenalectomy for a right adrenal mass. Pathology showed Adrenal gland, right, adrenalectomy: Adrenal cortical carcinoma, oncocytic variant. Tumor size 4.5cm, 45 Mitosis / 50 high power field, No lymphovascular invasion (LVI), Negative margins, necrosis, diffuse growth pattern, less than 25% clear cells, High nuclear grade. The patient was recommended for high dose Hydrocortisone and initiate Mitotane. Patient on hydroxychloroquine for rheumatoid arthritis.

She was tested for SARS-CoV-2 on March 24 due to prior exposure. The patient reported a temperature of 100.9 degrees Fahrenheit on March 25, for which she took acetaminophen 1g every 6 hours around the clock. She then developed a wet cough, productive of yellowish phlegm, and generalized body aches. Her breathing felt tight, though unlabored. The patient's test returned positive on March 26. She was then placed on a treatment break while she remained symptomatic. Her fever resolved, and only fatigue persisted by March 29. Moreover, the patient resumed treatment on March 31. Covid-19 PCR was positive on 3/24/20 and her antibody-positive IgG on 4/30/20.

Her husband had previously been diagnosed with Covid-19 pneumonia but was not on a ventilator and was getting better. The patient completed RT on 4/20/20 and feels well. No residual side effects from RT. The chest X-ray in May 2020 was clear. Patient notes being back to work full time.

Case 4

The patient is a 65-year-old female with FIGO Stage IV (TNM Stage: T3 N2 M1) endometrial carcinoma with sarcomatoid features. Prior history of cirrhosis and Hepatitis C. The Patient presented with post-menopausal bleeding and admitted to the hospital on April 2020-5/1/20. Work up, including an

endometrial biopsy, showed superficial fragments of high-grade malignant neoplasm with sarcomatous features. Transvaginal ultrasound showed pelvic ascites with multiple masses consistent with metastatic disease—thickened, heterogeneously nodular endometrium, likely the primary neoplasm. CT Abdomen and pelvis showed intrauterine 11.6 cm partially necrotic mass with extrauterine local invasion, suspicious for primary endometrial neoplasm. Extensive peritoneal tumor implants, with a dominant 8 cm pelvic implant. Splenic and hepatic capsular implants. 3.3 cm peripherally enhancing lesion contiguous with hepatic umbilical fissure; given plurality, tumor implant favored over intrahepatic primary or secondary neoplasm. Multiple bilateral solid pulmonary nodules, measuring up to 1.2 cm at the right lower lobe, suspicious for pulmonary metastases. Retroperitoneal metastatic lymphadenopathy. Liver cirrhosis with portal hypertension. Moderate ascites. The patient refused brain MRI but had CT of Brain, which as unremarkable. The patient was not deemed a surgical candidate. Palliative chemotherapy using carboplatin/Taxol was planned, and radiation was consulted for local treatment for continuing vaginal bleeding. The patient was treated to the pelvis/involved uterus/cervix using a 3D/conformal technique. The patient tolerated treatments quite well. She presented on 5/7/20 with cough, and a CXR revealed Low lung volumes. Interval development reticular densities left lung base possible discoid atelectasis. No consolidation effusion or pneumothorax. Ill-defined nodular density overlies cardiac silhouette (multiple nodules described on recent chest CT of April 28, 2020). The patient was diagnosed with Covid-19 during her treatment course. She did not require hospitalization.

Her vaginal bleeding improved toward the end of her treatment course. At 2000cGy, the course of radiation therapy was completed without any complications.

Case 5

A 76 y male with metastatic prostate cancer whose most recent treatment was to the T6-T10 vertebral body for pain palliation to a total dose of 8Gy in 1 fraction in May 2020. This treatment was delivered during his admission to the hospital when he was diagnosed with Covid-19 infection by PCR. The patient tolerated the RT treatment well and is responding with improved pain control in the treated region.

The patient is asymptomatic regarding his Covid-19 infection and is still hospitalized, pending a negative PCR test for COVID before discharge from the hospital. No adverse effects of RT.

Prior History

The patient initially presented with weak urine flow, hesitancy, frequency, and was found to have PSA 7.4. He underwent TRUS biopsy and subsequent radical prostatectomy in May 2014. The biopsy pathology showed adenocarcinoma 6/12 cores positive all in left side with two cores in left mid with Gleason 4+4 around 50% involvement, left apex one core Gleason 4+4 with around 60% involvement, one core in left apex and one core in left base positive for intraductal carcinoma around 20% and 5% involvement respectively, one core from left mid-Gleason 3+3 with less than 5% involvement, right base two cores with High-grade Prostate Intraepithelial Neoplasia. The patient underwent radical prostatectomy, and surgical pathology showed pT3a extra-prostatic extension, N0, margins involved by invasive carcinoma,

multifocal, 50% of prostate involved by tumor, primary pattern grade 5, secondary pattern grade 5, total Gleason score 8, LVI present, no seminal vesical involvement. The PSA was 1.2ng/ml in June 2014, 2.5ng/ml in August 2014. The patient was started on Lupron in August 2014, and his PSA was undetectable. The patient underwent radiation to the pelvis from Nov 2014 to Jan 2015 (records not available) and stopped Lupron in Feb 2015. PSA was 1.2ng/ml in October 2015, 2.5ng/ml in December 2015. The whole body bone scan on 12/11/2015 revealed multiple bone metastasis. The patient received 24Gy in 3 fractions of 8Gy to the left iliac bone in January 2020 for painful metastasis.

On 5/6/20, the patient received RT to T6-T10, 8Gy x1.

Other systemic treatments that the patient received includes Xtandi, Provenge, Zytiga. Also, the patient has undergone decompressive surgery for a cervical spine metastasis and cord compression. During the current hospital admission in April-May 2020, the patient was infected with Covid-19 on April 10, 2020. As of the last follow-up, the patient is in a rehabilitation center and has recovered from Covid-19 infection. The patient is being planned for Hospice care at this time. Other medical problems include Diabetes Mellitus, Deep venous thrombosis, and hypercalcemia secondary to osseous metastasis.

The 5 cases are summarized in Table 1.

Guidelines followed in our institution while treating patients that are COVID-19 positive.

For asymptomatic patients:

- Follow standard "ASK and MASK" guidelines at check-in – patients will be offered a mask anyway, even if asymptomatic, while in the department.

For known positive patients or patients awaiting test results:

- Must be treated the last patient of the day
- We will ask the patient to text department upon arrival to the parking lot and the patient will be given surgical mask and gloves upon arriving for treatment

o Staff members caring for patients will meet them outside of the building daily wearing full PPE (personal protective equipment): N95 respirator/surgical mask, isolation gown, and gloves (Figure 1).

o A staff member will escort the patient through the back of the department and enter through the exit door on the side of the radiation treatment room.

o If the patient needs to change into a gown for treatment, the patient will change inside of the treatment console to avoid exposure to other areas.

o Post-treatment, the patient will be escorted out of the department wearing a surgical mask.

o A staff member to remove all PPE post-treatment outside of the department and place it in a waste container with a lid to be discarded and perform hand hygiene.

Cleaning of Room after the patient leaves

- Room door must remain closed, and Room remains unoccupied for ONE hour before entering.
- All horizontal surfaces to be cleaned using GREY top PDI wipes by environmental services

Caring for more than one positive patient

- Cleaning instructions as outlined above must be followed in between 2 positive patients

o Room to remain unoccupied with the door closed for ONE hour

o All horizontal surfaces to be cleaned as per protocol above

Discussion

Our case series of 5 patients that were Covid-19 positive and received RT had outcomes that do not seem to be affected by this infection. There were no acute unexpected adverse effects noted in this group of patients versus those previously treated before this pandemic. Our report is the first reported series of Covid-19 infected cancer patients treated with RT. In the last five months, several published guidelines are being proposed for various malignancies. Select relevant studies that discuss challenges in cancer patients infected with COVID-19 are discussed below.

Recently published evidence suggests a higher rate of cancer in patients with Covid-19 infection compared to the general population. The report published in February from China showed a prevalence of 1% cancer in Covid-19 infected patients versus 0.29% in the general population. The most frequent site of malignancy was lung, and such patients were more likely to be older and smokers (1). This group of cancer patients was more likely to experience severe events when treated with chemotherapy or surgery. However, there were only 18 cancer patients identified in the study, and these small numbers combined with confounding factors such as COPD (chronic obstructive pulmonary disease) make the conclusions of the study unreliable (4).

Regarding managing cancer patients that develop Covid-19 infection, a modeling study (5) estimated the mortality and estimated the intensive care unit (ICU) requirements in Latin America patients, where the disease is now ravaging communities. A Markov model was constructed. Estimated ICU requirements for cancer patients maybe 12.7 days, the median time to mortality was 16.3 days, and the median time to severe events was 8.1 days. There will be an estimated 111,725 additional deaths of patients with cancer as a result of severe SARS-CoV-2 infection in the next two months, which is an increase of 18.5% in cancer-related deaths, compared with 2012.

A French registry study (6) to estimate the incidence of Covid-19 infections in breast cancer patients showed that 76 actively treated breast cancer patients out of 15,600 breast cancer patients had at least one consultation in the four months before lockdown. Fifty-nine patients were diagnosed with Covid-19, based on either a positive SARS-CoV-2 RNA test or radiologic findings. 10/59 (17%) were > 70 y age. Of the 59 Covid-19 patients, 47% were hospitalized, while 53% returned home. Eighty-two percent of the 28 hospitalized patients received antibiotics, and 11% received corticosteroids. At the last follow-up, four patients were transferred to ICU, and 76% were considered cured or recovering. 6.7% of patients died. One patient started endocrine therapy, and one patient received neoadjuvant chemotherapy.

A case report of a melanoma patient being treated with an immune checkpoint inhibitor (ICI) with nivolumab, from Germany was recently published (7). The patient was receiving adjuvant ICI after complete resection of stage IV melanoma. The patient developed mild/moderate fever but not respiratory compromise due to Covid-19 infection. Symptoms resolved spontaneously in 3 days—anti-PD-1 therapy for temporarily suspended but restarted after the patient recovered. The patient remains tumor-free.

In a published study from China (8), patients with CML (chronic myeloid leukemia) receiving TKI-therapy (tyrosine kinase inhibitor therapy) from Hubei Province were recruited from 29 centers of the Hubei Anti-Cancer Association, and an online questionnaire was distributed and collected by physicians at each. The questions included demographics, comorbidities, CML-related data including diagnosis, therapy and response, Covid-19 exposure history, and associated symptoms and treatment. The prevalence of Covid-19 was 0.9%, which was nine-fold higher than 0.1% reported in the general population's. 1/21 subjects receiving 3rd generation TKI developed Covid-19 versus 3/346 subjects receiving imatinib versus 0/162 subjects receiving 2nd generation TKIs (P = 0.096). Authors concluded that patients with no complete hematological response, with comorbidity, with 'advanced phase at diagnosis despite responding to TKI-therapy and those exposed to someone with SARS-CoV-2-infection might benefit from increased surveillance and possible protective isolation'.

A case series of 11 patients (9) describes the clinical course of patients that underwent thoracic surgery for malignancy in the early phase of the pandemic and were consequently diagnosed with COVID-19. Median days from surgery to Covid-19 infection was 13 (range 1–31 days), to death was 35 (range 5–42 days, n = 3), and to discharge upon recovery was 50 days (38–72 days, n = 8). Of the 11 confirmed cases, symptom onset included dry cough, dyspnea, and fever. In this group, Sars-CoV-2 may significantly increase the risk of death during the postoperative thoracic period. Case fatality (27.3%) was high and was significantly associated with resected lung segments (≥ 5), the severity of postoperative hypoproteinemia or hypoalbuminemia, and the peak value of lactate dehydrogenase.

In a case series of breast cancer patients (10) infected with Covid-19 from New York, 27 (0.6%) out of 4515, Covid-19 patients were diagnosed with breast cancer (BC). The median age of these BC patients was 56 years (range: 32–87). Comorbidities included hypertension, diabetes, and pulmonary disease. The majority had stage I to III BC, and 19% had metastatic disease. In the six months before Covid-19, 59% received chemotherapy, 44% hormone therapy, 22% HER2-directed therapy, 4% checkpoint inhibitor, 22%

had breast surgery, and 7% received RT. Treatment disruptions occurred in 74% of patients due to Covid-19. With a median follow-up from COVID diagnosis of 26 days (range 1–38), all patients were alive, except for an 87-year-old male with multiple comorbidities who received taxane-based chemotherapy for stage II BC seven days before symptoms.

There is a report of a patient on nivolumab for malignant melanoma that was well tolerated with no change in outcomes because of the Covid-19 infection (11). Another study evaluated the effects of PD-1 blockade on the severity of Covid-19 infection (12). A total of 60 consecutive patients with lung cancer that were COVID-19 positive were identified for the study between March-April 2020, of which 41 (59%) received PD-1 blockade. Four categories were identified: Patients that received PD-1 blockade at any time, PD-1 blocker within the last six months, within the prior six weeks, and first dose within three months. Overall, there was no significant difference in the severity of COVID-19 irrespective of the start date of PD-1 blockade. When adjusted for smoking history and gender, the impact of PD-1 on hospitalization, ICU/intubation/DNI, and death was not significant.

In an Italian study of 25 patients with a cancer diagnosis that were infected with Covid-19 (13), a total of 52% had long term smoking history, 76% had several comorbidities such as diabetes mellitus, hypertension, and chronic obstructive pulmonary disease. The mean age was 71 years (range 50–84 years). The most common tumor site was lung (32%) followed by gastrointestinal (24%), genitourinary (24%), breast cancer (8%), hematologic tumor (8%), and unknown primary site (4%). Forty-eight percent of patients were treated with anticancer therapy, 66.67% with chemotherapy, and 33.33% with immunotherapy, while 52% were not on any anticancer treatment. All patients with gastrointestinal cancer and 75% of patients with lung cancer recovered from infection and were alive when the report was published. Patients receiving immunotherapy for lung cancer were alive. Patients that received hydroxychloroquine did better than those that did not. Thirty-six percent died, and 64% were alive while in the control group of patients without cancer, 16% died, and 84% were alive, which was not statistically significant.

Conclusion

Our study is the first reported case series of cancer patients that were Covid-19 positive and received RT. Our limited experience suggests no added toxicity during COVID-19 infection, although long term data is pending. This series and guidelines followed in our institution for RT delivery of COVID-19 positive patients can be used by other institutions in similar situations. As additional information is obtained about Sars-Cov-2 and its impact on the course of cancer through larger studies, recommendations regarding RT may change. In the future, prospective studies using RT in Covid-19 patients will be ideal.

Abbreviations

Gy: Gray

COVID-19: Coronavirus disease -2019

Sars-cov-2: Severe acute respiratory syndrome coronavirus 2

RT: Radiation therapy

IMRT: Intensity modulated radiation therapy

CRT: Chemoradiation therapy

CT: Computerized tomography

PET-CT: Positron emission tomography- Computerized tomography

FIGO: International Federation of Gynecology and Obstetrics

O2: Oxygen

2L: 2 liters

HDR: High dose rate

SCC: Squamous cell carcinoma

IVC: Inferior vena cava

cGy: Centi-gray

PCR: Polymerase chain reaction

ACTH: Adrenocorticotropic hormones

WNL: Within normal limits

LVI: Lympho-vascular invasion

IgG: immune-globulin

PSA: Prostate specific antigen

T6-T10: Thoracic 6th vertebrae- Thoracic 10th vertebrae

PPE: Personal protective equipment

ICU: Intensive care unit

ICI: immune-checkpoint inhibition

PD: Programmed cell death

CML: Chronic myeloid leukemia

TKI: Tyrosine kinase inhibitor

BC: Breast cancer

DNI: Do not intubate

Declarations

Ethical Approval and Consent to participate

The study was approved by IRB as a part of ONCORA data collection. The ethical approval and consent for this retrospective data collection was waived.

Consent for publication

Consent to publication obtained as a part of ONCORA datacollection.

Availability of supporting data

All data generated or analyzed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

All authors read and approved the final manuscript. BP and LP involved in design, analysis and writing the manuscript. JA, LL, CM, AN involved in data collection and writing the manuscript.

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Table

Table 1: Covid-19 positive patients receiving RT

Case #	Primary site	Site of RT	Total dose/Dose per fraction	Intent	Alive/Died	Comments
1	Cervix	Cervix plus nodes	21.6Gy/1.8Gy/f Planned 45Gy	Curative	Died	Possible perforation. Died of pulmonary symptoms secondary to covid-19
2	Vulvar cancer	Vulva plus nodes	56Gy/2Gy/f Planned 64Gy	Curative	Alive	Stopped treatment at 56Gy due to poor nursing home care. Clinical complete response
3	Adrenocortical carcinoma	Adrenal bed	45Gy/1.8Gy/f	Curative postoperative	Alive	Doing well
4	Endometrial	Uterus	20Gy/4Gy/f	Palliative	Alive	Doing well, bleeding stopped
5	Prostate	Thoracic spine	8Gy/8Gy x1 f	Palliative	Alive	Doing well. Planned for hospice

Abbreviations: Gy: gray, f: fraction

Figures

Figure 1

Radiation Departmental staff in full PPE prior to patient treatment