

# How COVID-19 pandemic affected cancer progression: Three different scenarios evidenced by PET imaging

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## Abstract

COVID-19 pandemic is having a strong impact on healthcare providers around the world, by refocusing and reducing non-essential medical activities. Nuclear medicine departments among others, have been reorganizing and reprioritizing diagnostic and therapeutic procedures. This reorganizing had a negative impact on the supply of positron emission tomography (PET) services to oncologic patients, whose health was affected. We herein present the PET findings in three different cancer scenarios in which disease course was dramatically affected by the COVID-19 outbreak.

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## Introduction

Following the emergence of a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an unprecedented and unforeseen worldwide outbreak of coronavirus disease 2019 (COVID-19), resulted in what we are now witnessing: a pandemic, as was officially declared by the World Health Organization on March 11. A variety of critical and restrictive measures have been implemented by governments around the world to soften the impact on institutions, global economy and most importantly medical services. Frontline healthcare providers are diving into unexplored territories and facing difficult decisions. The constant focus on infectious disease and intensive care units due to COVID-19, gravely reduced the focus on other non-essential healthcare activities.

Daily clinical practice in Nuclear medicine (NM) departments has been adapted and protective measures to minimize the risk for staff, patients and family members have been implemented. The number of procedures (exams and treatments) has been reduced by identifying and prioritizing those that are essential. Postponing non-essential procedures as well as research activities is to be considered [1]. To ensure an uninterrupted supply of positron emission tomography (PET) services to oncologic patients is of great importance. Postponed diagnosis and detection of recurrent disease, as well as treatment delays, can have deleterious effects on the disease outcome in this specific group of patients. Several epidemiological studies during the COVID-19 pandemic, showed that patients with cancer are particularly vulnerable and present a higher risk for SARS-CoV-2 infection with more severe disease course, mostly due to a compromised immune response following various anticancer treatment modalities [2, 3]. An additional increase in the risk of exposure and viral infection comes from commuting and regular hospital visits. As a result, reducing treatment intervals, switching to oral medications when possible or temporarily postponing anticancer treatment has been recommended [4]; with an appropriate individual assessment of the risk versus the potential benefit in the evolution of the primary neoplastic disease.

Here, we present three cases of patients referred to our unit for a PET evaluation in the time of COVID-19 crisis. Unfortunately, all of them exhibited a progression of the neoplastic disease following a decision for temporary treatment discontinuation; yet the rationale behind this particular decision was different for each patient.

## Case 1

A 43-year-old female patient was first diagnosed with invasive mixed ductal and lobular breast cancer in 2012. Initial treatment included surgery, chemotherapy and radiothe-

rapy at the level of the breast. Five years later the disease recurred with massive bone marrow, liver and lymph node metastatic infiltration. In the following period, various types of systemic as well as palliative radiation therapy on multiple bone metastatic locations were administered. Additionally, brain metastatic lesions were diagnosed in the beginning of year 2019. Finally, after 3 cycles of third line of chemotherapy with doxorubicin, there was good partial metabolic response seen on a follow-up fluorine-18-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) PET/computed tomography (CT) scan performed in December 2019 (Figure 1A). The treatment continued for 3 more cycles, the last one being administered in mid-February. By the time the next chemotherapy cycle was supposed to be scheduled, due to the already imposed COVID-19 related critical situation, a decision to stop treatment was made based on the patient's wish to stay confined and to minimize the risk of SARS-CoV-2 infection. Three months later, a follow-up  $^{18}\text{F}$ -FDG PET/CT scan was performed in order to assess the disease evolution while treatment was suspended, revealing an overall metabolic and morphologic progression of all known lesions (Figure 1B), leading to a new line of chemotherapy with eribulin.

### Case 2

A diagnosis of prostate adenocarcinoma with a Gleason Score of 6, stage IIb, was first made in 2010 in a 72-year-old patient, treated with radiotherapy. Local recurrence occurred 5 years later, so the patient was placed under hormone therapy with flutamide, remaining stable up until the beginning of 2019, when treatment needed to be changed to enzalutamide due to biological and radiological progression. At the end of the same year, further progression was revealed on prostate specific membrane antigen (PSMA) PET/CT with appearance of new bone and lymph node metastases (Figure 2A). At that point, chemotherapy with docetaxel was initiated with a baseline Prostate-Specific Antigen (PSA) at 24 ng/mL. Good biological response was noted after completing the 4th cycle of chemotherapy, with PSA nadir of 14.9 ng/mL. However, in the context of the COVID-19 pandemic, the patient was considered as high risk for SARS-CoV-2 infection, so the treatment was temporarily stopped. The follow-up PSMA PET/CT performed 3 months later, showed evidence of disease progression with an extensive bone metastatic spread (Figure 2B), in accordance with a biological progression of serum PSA now rising to 36.5ng/mL. Thus, an imminent need to restart the treatment with chemotherapy was acknowledged by the oncological team as well as the patient.

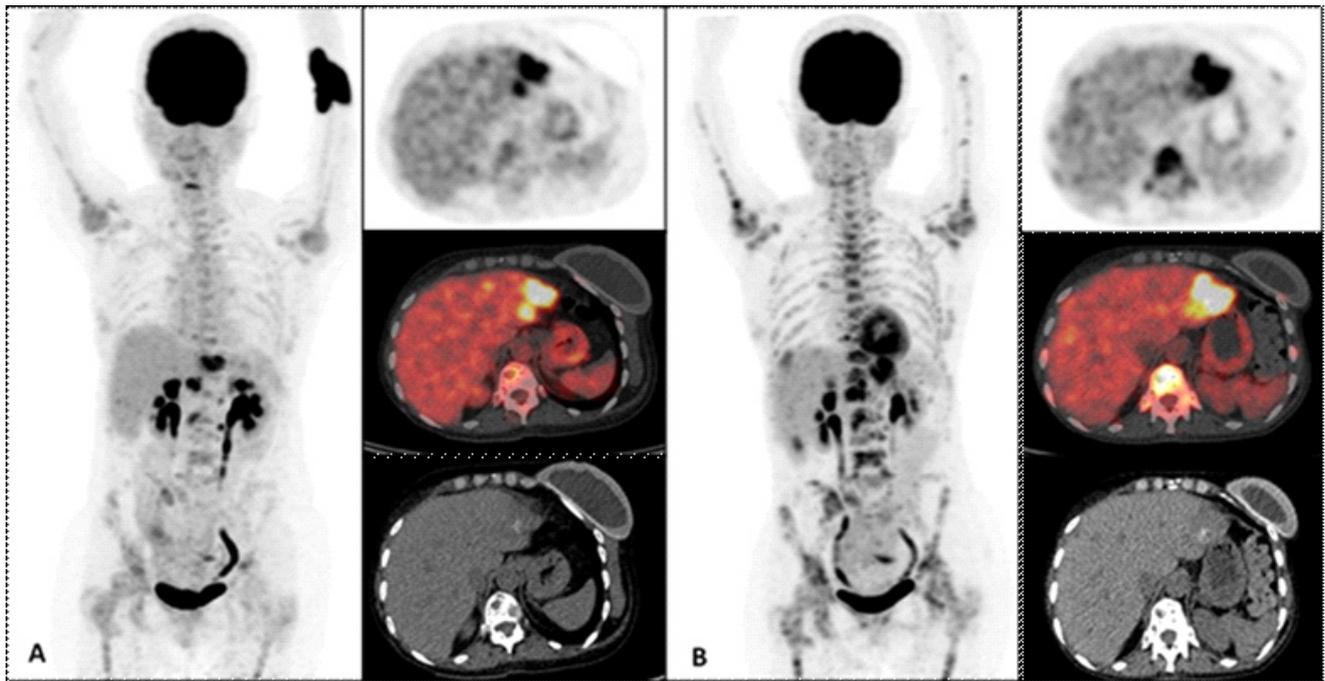
### Case 3

As part of a routine follow-up, four months after the start of nivolumab in the treatment course of a metastatic renal cell carcinoma (RCC) in a 51-year-old male patient, an  $^{18}\text{F}$ -FDG PET/CT scan was performed in our institution. Initially the diagnosis of a chromophobe RCC of left congenital solitary kidney, was made in 2011 and was treated first by partial and then by total left nephrectomy in the following year. Different treatment modalities were introduced between time of

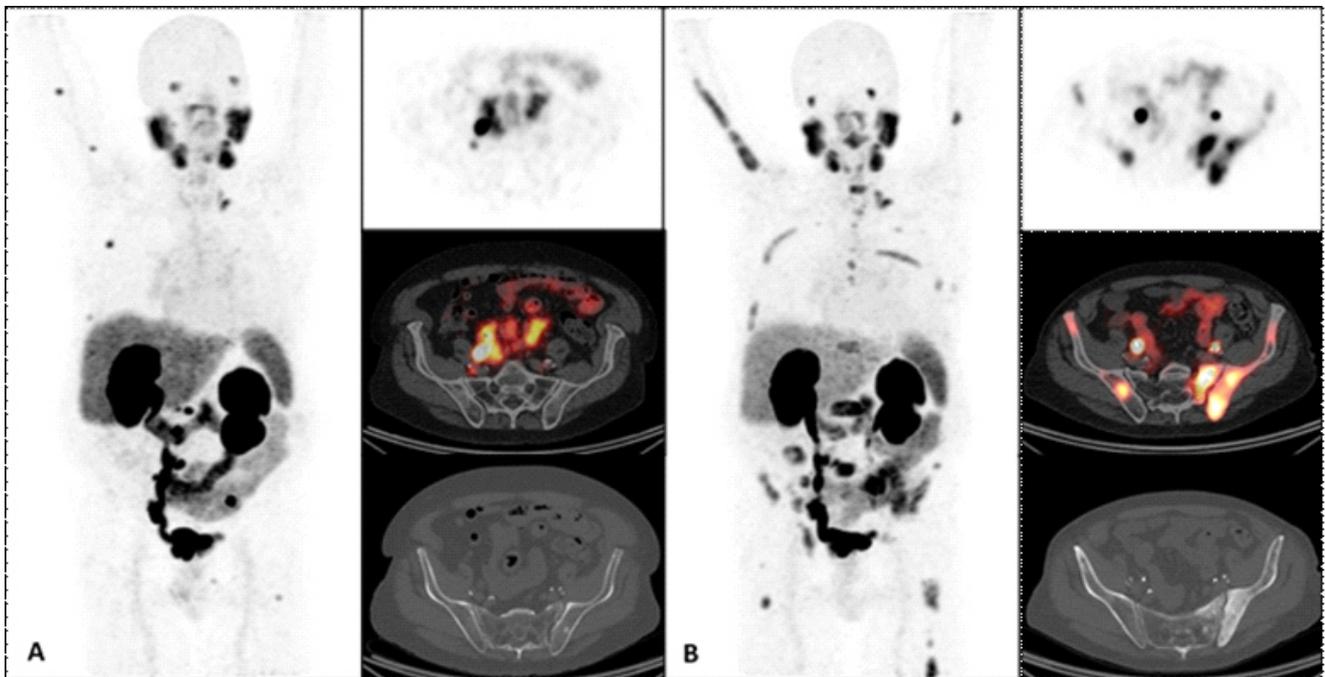
diagnosis and December 2019, when progression was revealed under 3<sup>rd</sup> line of treatment with everolimus. A shift towards immunotherapy with nivolumab was made at that point, with good response on early assessment (Figure 3A). However, the follow-up  $^{18}\text{F}$ -FDG PET/CT scan performed in the peak of the COVID-19 outbreak, showed a suspicion of metabolically active viral infection in an already symptomatic state, based on the presence of multiple hypermetabolic ground-glass opacities with bilateral lung involvement (Figure 4A) [5]. The patient was hospitalized the same day and SARS-CoV-2 infection was confirmed. Consequently, the next courses of nivolumab were canceled. As soon as the patient fully recovered, nearly two months later, treatment was reintroduced and an  $^{18}\text{F}$ -FDG PET/CT was performed to assess the extent of the metastatic disease. While the inflammatory reaction in the lungs was improving, the break from nivolumab had taken its toll on the cancer spread (Figure 3B, Figure 4B). New line of treatment with the tyrosine kinase inhibitor cabozantinib was initiated.

## Discussion

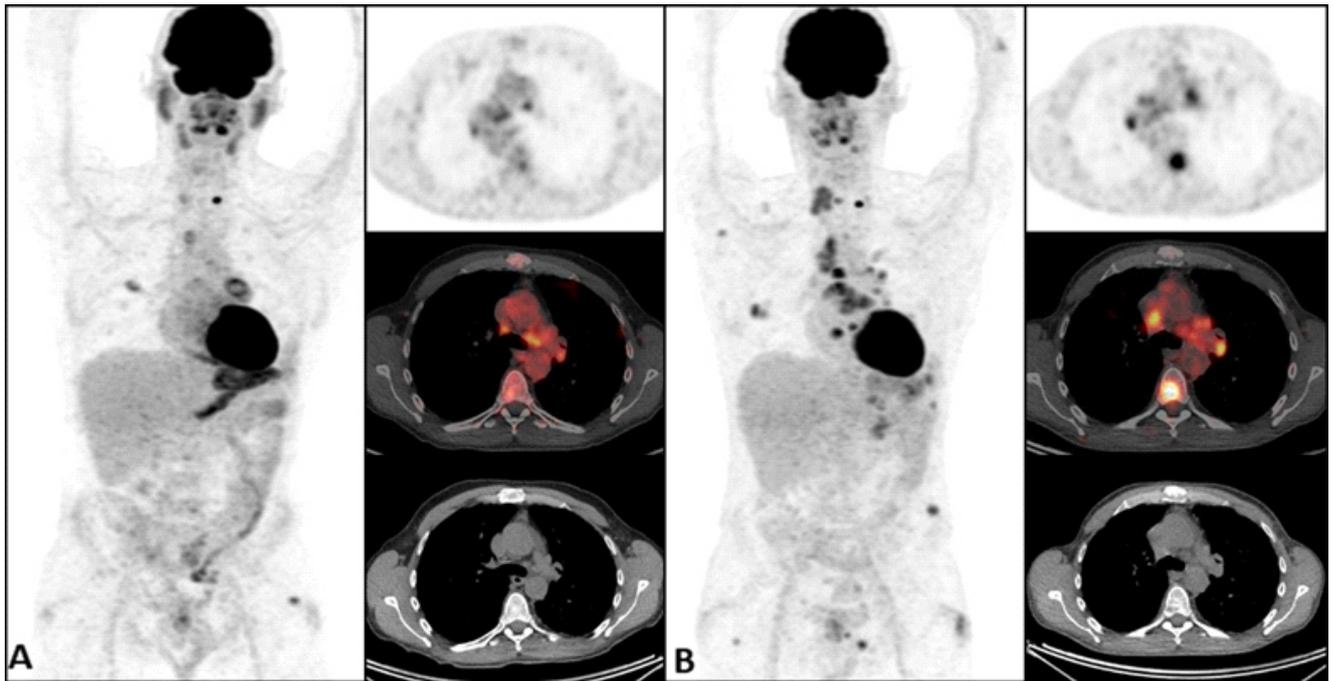
In the midst of the COVID-19 pandemic, despite having to reduce the number of diagnostic and therapeutic activities, NM departments are still expected to continue to provide necessary services. Special consideration is given to oncological patients, where accurate staging, early detection and localization of recurrent disease or disease progression is crucial and oftentimes relies on performing serial PET scans. Oncological societies have rapidly provided recommendations on how to approach and prioritize patients on systemic anti-cancer treatments during the outbreak, as well as to seek alternative methods to monitor those patients without having to increase the risk of exposure by coming to hospital wards [4, 6]. Dietz et al. (2020) suggested individualized priority categories for breast cancer patients' care [7], while a medical group from Milan, Italy presented their personalized strategies to assess the risk-benefit ratio for this group of patients, taking into consideration the risk of SARS-CoV-2 infection based on current epidemiological situation and the risk of developing serious illness due to comorbidities [8]. However, in our breast cancer patient the proper individual risk estimation might have been affected by the patient's wish to stay confined and her refusal to make the necessary hospital visits for the chemotherapy courses. Maintaining anticancer treatment during the COVID-19 outbreak, by itself holds an increased risk of infections due to patients' immunosuppressive state [9]. Therefore, a delicate decision to temporarily post-pone treatment and reevaluate in a timely manner has been frequently made, ideally not at the expense of the cancer spread (i.e. in Case 2). However, recently published data from a prospective study analyzing the interaction between anti-cancer treatments and COVID-19 morbidity and mortality in 800 cancer patients, showed that chemotherapy (as well as immunotherapy, hormonal therapy, targeted therapy or radiotherapy) administered



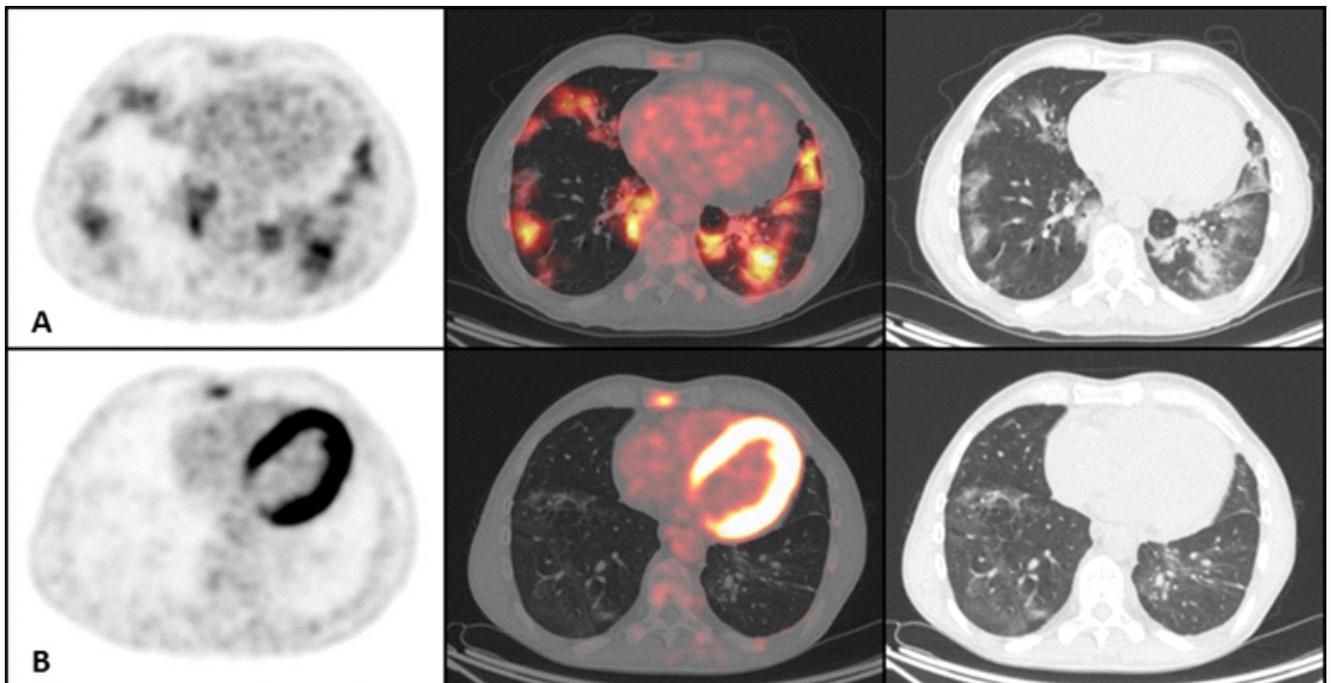
**Figure 1.** Maximum intensity projection and axial PET and fused PET/CT images of two <sup>18</sup>F-FDG PET/CT scans, showing disease status prior to interrupt doxorubicin (A) followed by a clear progression after four months of therapeutic break (B) in a breast cancer patient.



**Figure 2.** Maximum intensity projection and axial PET and fused PET/CT images of two PSMA PET/CT scans, A: At beginning of treatment with docetaxel, and B: After 2-months of therapeutic break showing disease progression with an extensive bone metastatic involvement.



**Figure 3.** Maximum intensity projection and axial PET, fused PET/CT and CT images showing A: Early response to treatment, and B: Progression of bone and lymph node metastases due to 2-months long therapeutic break in a patient with renal cell cancer.



**Figure 4.** Axial PET, fused PET/CT and CT images of lower lung lobes, showing (horizontally) A: High <sup>18</sup>F-FDG uptake in ground-glass opacities in both lungs, consistent with an active SARS-CoV-2 infection and B: Near complete resolution of the lung lesions two months later, but a progression of bone metastatic lesions in a patient with renal cell cancer.

not significantly associated with increased mortality. Therefore, this provides arguments to the oncological community not to postpone effective anticancer therapies in these times of crisis [10]. Furthermore, cancer patients should maintain all their scheduled diagnostic tests, including  $^{18}\text{F}$ -FDG PET/CT, without unnecessary delays [11]. Fluorine-18-FDG PET/CT scans have proved to be a valuable additional tool to detect active SARS-CoV-2 infections in cancer patients, when an  $^{18}\text{F}$ -FDG PET/CT is being performed as part of a routine follow-up [12, 13]. In such cases, a temporary discontinuation of the treatment is usually necessary. An additional  $^{18}\text{F}$ -FDG PET/CT evaluation of the disease status once the infection has resolved and before treatment is reinstated, could prove equally important for the therapeutic management.

In conclusion, COVID-19 has had a profound impact on cancer patients' care, especially since continuous PET/CT examinations are of the utmost importance. As a highly sensitive and one-step whole body hybrid technique to evaluate the functional and morphological status of both the oncological disease and presence of potentially active COVID-19 lung abnormalities, the PET/CT findings can be used as a very strong argument in the decision of whether or not a treatment should be discontinued. Thus; even at a time of crisis, an effort to keep the routine daily practice in PET should be made.

The authors declare that they have no conflicts of interest.

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