




The impact of the COVID-19 pandemic on oncological disease extent at FDG PET/CT staging: the ONCOVIPET study

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Abstract

Purpose To investigate whether the COVID-19 pandemic and national lockdown had an impact on the extent of cancer disease at FDG PET/CT staging as surrogate marker.

Methods Retrospective observational study including cancer patients submitted to FDG PET/CT staging from June 1 to October 31, 2020, and June 1 to October 31, 2019, respectively. Data regarding primary tumour, nodal (N) status and number of involved nodal stations, and presence and number of distant metastases (M) were collected. Each scan was classified in limited vs advanced status. Data were aggregated across the study population and tumour type. Bi-weekly frequencies of the observed events were analysed.

Results Six hundred eleven patients were included (240 in 2019 vs 371 in 2020, respectively). A significant increase of advanced disease patients (rate 1.56, $P < 0.001$), N+ or M+ patients (rate 1.84 and 2.09, respectively, $P < 0.001$), and patients with a greater number of involved N stations or M (rate 2.01 and 2.06, respectively, $P < 0.001$) were found in 2020 compared with data of 2019. Analysis by tumour type showed a significant increase of advanced disease in lymphoma and lung cancer in 2020 compared with 2019 ($P < 0.001$). In addition, a significant increase of nodal involvement was found in lung, gastro-intestinal, and breast cancers, as well as in lymphoma patients ($P < 0.02$). A significant increase of distant metastases was found in lung cancers ($P = 0.002$).

Conclusion Cancer patients with advanced disease at FDG PET/CT staging increased in 2020 compared with 2019, following the national lockdown due to the COVID-19 pandemic, 1.5-fold with a significant increase of patients with N or M involvement. Targeted health interventions are needed to mitigate the effects of the pandemic on patient outcome.

Keywords COVID-19 · FDG · Oncology · Pandemic · PET · Staging

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Introduction

The global coronavirus disease 2019 (COVID-19) pandemic has severely affected healthcare systems, economy, work, education, and social relationships. On March 2020, National Health Services (NHSs) of many countries, starting with Italy, suddenly redesigned their services to increase the capacity for treating patients with COVID-19. Procedures included discharging thousands of inpatients to free up beds, postponing scheduled treatments, shifting appointments online whenever possible, and redeploying healthcare staff. In addition, on March 9, 2020, the Italian Government declared a national lockdown in response to the COVID-19 pandemic, which lasted until May 18, 2020. “Stay-at-home” orders were enacted to slow the spread of

the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and reduce the burden on the NHS. Consequently, the COVID-19 emergency had direct and indirect effects on the healthcare delivery process. Direct effects included the radical reorganization of health systems to respond to the acute needs of people infected with the SARS-CoV-2 and to contain the infection protecting the most vulnerable categories and healthcare personnel. Indirect effects of the pandemic are represented by the impact on people with acute and non-acute conditions not related to COVID-19, especially cardiovascular and oncological diseases [1–7]. In oncology, the best outcomes are obtained in those tumours diagnosed at an early stage and treatment is started straight away. Unfortunately, several diagnostic and treatment pathways, used for cancer patient management, have been severely affected, especially during the “first wave” of the COVID-19 pandemic [8–11]. In addition, the fear of COVID-19 transmission contributed to a lower propensity of patients with symptoms to refer directly to hospitals. Therefore, many patients likely experienced a delay in both diagnosis and treatment of cancer. To date, no direct population-based evidence of the impact of the COVID-19 pandemic on the extent of cancer disease at staging is available. Positron emission tomography/computed tomography with 2-deoxy-2-[18F] fluoro-D-glucose (FDG PET/CT) has become one of the cornerstones of patient management in oncology. The high diagnostic accuracy of FDG PET/CT at staging to detect lymph node and distant metastasis and the impact on patient management has been widely reported in several malignancies [12–24]. This study aims to evaluate whether the delay in cancer diagnosis and initial staging, due to the COVID-19 pandemic and its consequent national lockdown, had an impact on disease extent in cancer patients using FDG PET/CT staging as surrogate measure.

Materials and methods

Population, selection criteria, and data extraction

We conducted a single-centre retrospective observational study including all consecutive oncological patients submitted to whole-body FDG PET/CT staging at the PET-CT Centre of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome, Italy, in two selected intervals: June 1 to October 31, 2019, and June 1 to October 31, 2020. These intervals were selected to evaluate effects of any diagnostic delays on disease extent at time of initial staging due to the first pandemic wave and the restrictions enforced during the national lockdown from March 9 to May 18, 2020. This study was approved by the local ethics committee (No. 4024), and informed consent was obtained from all patients included in the study. Patients' information

was retrieved from internal medical records and PET/CT images. Only patients ≥ 18 years of age with a cancer diagnosis and FDG-avid tumours, who performed a whole-body PET/CT for staging purposes, were included in the study. Patients performing PET/CT for restaging purposes (e.g., suspected recurrence, therapy response evaluation) or with radiopharmaceuticals other than FDG were excluded. FDG PET/CT images of all included patients were retrieved from the Institution's Picture Archive and Communication System and displayed on a dedicated workstation using the software Syngo.via (Siemens®). All included patients were divided into sub-groups according to the primary tumour (i.e., lung, head and neck, gynaecologic, gastro-intestinal, breast, lymphoma, melanoma, and myeloma). PET/CT images were evaluated independently by 2 nuclear medicine physicians for each tumour sub-group referring to the report previously drawn up to assess the disease stage according to the International Classification of Diseases for Oncology (American Joint Committee on Cancer staging manual) [25]. Information regarding patients' gender, age, date of PET/CT scan, site, and histology of primary tumour (T), presence/absence of lymph node (N +/N0) involvement and number of involved nodal stations, presence/absence of distant metastases (M +/M0), and number of metastatic lesions was collected. Myeloma patients were excluded from nodal assessment because of the very rare nodal spreading of the disease. In lymphoma patients, all extranodal disease sites were considered metastases for statistical analysis. Based on the number of distant metastases, including extranodal disease sites in lymphomas, a 4-point scale—0 (no distant metastases), 1 (1 to 3 lesions), 2 (4 to 7 lesions), and 3 (> 7 lesions)—was used. Based on this evaluation, all PET/CT scans were categorized in advanced or limited disease stages: advanced stage (III and IV) or limited stage (I and II) for breast, gynaecologic, lung, and head and neck cancers, lymphoma, and melanoma; advanced stage (any T, any N, M1) or limited stage (M0) for gastro-intestinal cancers; and advanced stage (extra-skeletal disease and/or presence of lytic lesions on CT) or limited stage (no extra-skeletal disease, no lytic lesions on CT) for myeloma. Additionally, to confirm PET tumour staging, information on the subsequent patient management was reviewed (e.g., medical records referred to tumour multidisciplinary boards, subsequent examinations performed, type of treatment).

Statistical analysis

Data were gathered in the study population and tumour type generating bi-weekly frequencies for the observed T, N, and M events, the number of N stations and M sites, and tumours in advanced status. This was done because the updates of the national health surveillance were provided bi-weekly and the standard quarantine period covered a

15-day period. Poisson models were fitted to investigate how the years 2019 vs 2020 affected the observed frequencies. For each model, the year was used as a binary predictor, and the exponential transformation of the coefficient was interpreted as rate. Of note, this study has not analysed the incidence of tumour or advance disease. In fact, the Poisson models have been fitted without the offset term and returned coefficients (in exponential terms) interpretable as rate. We assumed that hospital user base across the year is very similar. Finally, myeloma and head and neck tumours were analysed by Firth's logistic regression modelling [26] or small samples because of very low or null counts in response variables. In these cases, binary outcomes were considered (0 = counts null, 1 = counts not null), and the exponential transformation of the coefficient was interpreted as odds ratio. *P* values less than 0.05 indicated significance. All the analyses were performed using R statistical environment (version 4.0.3).

Results

Three thousand five hundred fifty-one and 3443 FDG PET/CT scans were performed in our centre from June 1 to October 31, 2019, and from June 1 to October 31, 2020, respectively (Fig. 1). According to the inclusion and exclusion criteria, 240 patients in 2019 and 371 patients in 2020 were finally included in the study. The main characteristics of study population are described in Table 1. Table 2 shows the bi-weekly frequencies for the observed T, N+, and M+ events, the number of N stations and M sites, and tumours in advanced status over the two reference periods.

Fig. 1 Flowchart of FDG PET/CT scans from June 1 to October 31, 2019, and from June 1 to October 31, 2020

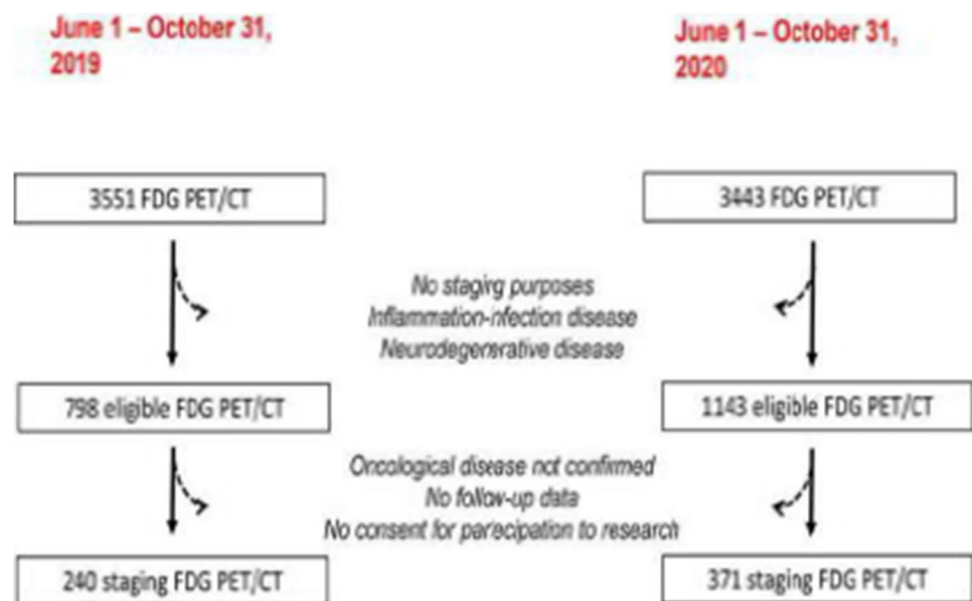


Table 1 Study population characteristics (*n*=611)

	June 1–October 31, 2019	June 1–October 31, 2020
<i>n</i>	240	371
Age (yrs), mean ± SD	63 ± 14	63 ± 15
Male, <i>n</i> (%)	106 (44)	157 (42)
Tumour type, <i>n</i> (%)		
Lung	75 (31.3)	112 (30.2)
Gynaecologic	53 (22.1)	76 (20.5)
Gastro-intestinal	36 (15)	47 (12.7)
Lymphoma	32 (13.3)	67 (18.1)
Breast	16 (6.7)	26 (7)
Head & neck	15 (6.2)	20 (5.4)
Myeloma	10 (4.2)	12 (3.1)
Melanoma	3 (1.2)	11 (3)

n frequency, *SD* standard deviation

Advanced vs limited disease at FDG PET/CT staging

Overall, the bi-weekly analysis of ranges showed a significant increase in the rate of advanced tumours in 2020 compared with 2019 (rate 1.56; 95% confidence interval [CI] 1.23–1.97; *P* < 0.001).

Nodal and metastatic disease at FDG PET/CT staging

Overall, the bi-weekly analysis demonstrated a significant increase in the rate of N+ or M+ patients in 2020 compared with 2019 (N+: rate 1.85, 95% CI 1.50–2.27, *P* < 0.001; M+: rate 2.09, 95% CI 1.55–2.82, *P* < 0.001). The rate of patients

Table 2 Bi-weekly frequencies (11 intervals) for the observed T, N+, and M+ events, the number of N stations and M lesions, and tumours in advanced status in 2019 and 2020

2019 intervals	T [#]	N+	M+	N stations	M sites*	Advanced disease
1	34	25	10	111	16	21
2	24	12	8	51	20	15
3	11	11	5	42	10	8
4	17	13	7	38	10	10
5	16	10	5	23	9	8
6	18	12	4	29	6	12
7	19	13	10	75	13	13
8	10	10	5	43	8	7
9	20	13	4	21	5	7
10	10	12	4	67	4	7
11	8	7	2	17	2	6
2020 intervals	T [#]	N+	M+	N stations	M sites*	Advanced disease
1	14	19	8	67	14	11
2	27	21	12	93	23	16
3	28	25	11	92	21	18
4	26	23	9	81	10	17
5	26	25	14	101	24	20
6	25	20	10	92	17	14
7	21	25	17	151	23	19
8	25	20	10	74	13	15
9	28	25	15	103	27	15
10	30	25	14	76	21	14
11	25	27	14	107	20	19

[#]T cases represent solid tumours only; *extranodal sites of lymphoma patients were included in the M analysis as reported in the “Materials and methods” section

with a higher number of involved N or M stations resulted significantly increased in 2020 compared with 2019 (rate of N stations: 2.01, 95% CI 1.80–2.23, $P < 0.001$; rate of M sites: 2.06, 95% CI 1.63–2.61, $P < 0.001$).

Analysis by tumour type

The bi-weekly frequency analysis demonstrated a significant increase in advanced disease, N+ and M+/extranodal rate, and number of involved N stations and M sites for both lung cancer and lymphoma in 2020 compared with 2019 (Table 3). Compared with 2019, advanced disease rate significantly decreased in 2020 in gynaecologic cancer. Nodal involvement resulted increased in gastro-intestinal and breast cancers. Figures showing bi-weekly frequency distribution of advanced disease status, N+, M+, and number of nodal stations involved and distant metastases at FDG PET/CT staging are provided in the Supplementary Material (Fig. 2–6).

Discussion

The results of our study show that the rate of cancer patients with advanced disease at time of FDG PET/CT staging was 1.5-fold higher in 2020 compared with 2019, following the

national lockdown due to the COVID-19 pandemic. In addition, we found approximately a twofold increase at staging in the rate of cancer patients with nodal involvement or metastatic disease and with a greater number of involved nodes or distant metastases. In 2020 compared with 2019, patients with lung cancer and lymphoma showed a significant (1.9 to 2.6-fold) increase at staging in advanced disease rate, nodal/extranodal involvement, metastatic status, and number of nodal stations and metastatic/extranodal sites. In addition, gastro-intestinal and breast cancers showed a significant increase of nodal involvement in 2020 compared with 2019. However, gynaecological cancers showed a significant decrease in advanced disease rate at staging in 2020 vs 2019. This retrospective observational study indirectly analysed the impact of the first COVID-19 pandemic wave and its national lockdown on the extent of cancer disease at staging using whole-body FDG PET/CT as a surrogate marker. Oncological FDG PET/CT is known to be the most accurate non-invasive technique for cancer staging in most histotypes because of its superiority over radiological imaging, mainly in assessing lymph node involvement and distant metastases [12]. From our data, more cancer patients showed an advanced disease stage at time of FDG PET/CT staging in 2020, after the national lockdown, compared with the same reference period in 2019. An increased rate of patients with

Table 3 Bi-weekly analysis results for tumour type (2020 vs 2019)

	Rate	95% CI	<i>P</i> value
Lung cancer			
Advanced stage	1.92	1.3–2.8	<0.001
N+	1.97	1.3–2.9	<0.001
M+	2.25	1.3–3.8	0.0025
N (n.)	2.30	1.8–2.8	<0.001
vM (n.)	2.55	1.7–3.8	<0.001
Lymphoma			
Advanced stage	2.68	1.5–4.8	<0.001
N+	2.42	1.5–3.8	<0.001
Extra nodal +	2.31	1.3–3.9	0.0022
N (n.)	2.15	1.8–2.5	<0.001
Extra nodal (n.)	2.59	1.5–4.3	<0.001
Gastro-intestinal cancer			
Advanced stage	1.63	0.7–3.4	0.1981
N+	1.99	1.1–3.5	0.0163
M+	1.62	0.6–3.9	0.2799
N (n.)	1.68	1.1–2.4	0.0053
M (n.)	1.49	0.7–2.8	0.2090
Breast cancer			
Advanced stage	1.24	0.4–3.1	0.6380
N+	1.90	0.9–3.9	0.0823
M+	3.49	0.7–16.8	0.1181
N (n.)	2.66	1.6–4.4	0.0001
M (n.)	2.99	0.9–9.3	0.0570
Gynaecologic cancer			
Advanced stage	0.48	0.2–0.8	0.0209
N+	1.45	0.9–2.2	0.1103
M+	2.19	0.7–6.3	0.1437
N (n.)	1.31	0.9–1.7	0.0576
M (n.)	0.99	0.4–2.3	0.9999
Head & neck tumour			
Advanced stage	0.68*	0.1–4.1	0.6790
N+	0.63*	0.1–4.5	0.1103
M+	0.50*	0.1–2.8	0.4350
N (n.)	0.63*	0.1–4.5	0.6529
M (n.)	0.50*	0.1–2.8	0.4350
Myeloma			
Advanced stage	2.28*	0.3–15	0.3950
M+	2.87*	0.5–16.7	0.2402
M (n.)	2.87*	0.5–16.7	0.2402

N+ presence of nodal involvement, M+ presence of metastatic disease; N (n.) number of nodal stations, M (n.) number of metastatic sites grouped using a 4-point scale (0 [no distant metastases], 1 [1 to 3 lesions], 2 [4 to 7 lesions] and 3 [>7 lesions]); *Odds ratio obtained by Firth's logistic regression models. In bold are the significant results ($P < 0.05$)

The rates (or odds ratio), 95% CIs, and *P*-values are returned by Poisson or Firth's logistic regression modelling, applied to the bi-weekly data (i.e., statistical units). The predictor of the statistical models is the binary variable regarding the year (2019 vs 2020)

nodal involvement and metastatic disease was also demonstrated. This increase might be explained with delays in accessing cancer diagnosis for many patients correlated to the COVID-19 pandemic. The first phase of the emergency determined a reduction in inpatient and outpatient services provided to non-COVID patients, i.e. delays or suspensions of important screening programmes, limitations of some diagnostic tests such as CTs in the emergency context and cancellations or delays of specialist visits, and some elective procedures such as biopsies or surgeries [27–31]. Several European countries reported a drop of 15 to 40% of diagnostic cancer rates at the beginning of the pandemic. In Italy, approximately 1.4 million fewer screening exams were performed in the first 5 months of 2020 compared with the same period in 2019 [32]. Surgery was the most affected modality having been delayed or cancelled in over 10% of patients in 34% of European Centres [11]. In Italy, a significant decrease (20–50%) in the volumes of screening tests, outpatient specialist visits, and oncological interventions was reported in 2020 compared with 2019, even in geographical areas where a lower incidence of the SARS-CoV-2 was recorded during the first wave of the pandemic [32]. In addition to limited diagnostic capacity and patient admissions, many patients were reluctant to visit hospitals out of fear being infected or they preferred to postpone elective care according to public health measures encouraging people to stay at home. The quarantine and financial difficulties due to the lockdown had also an impact on travel and care-seeking behaviours. In fact, the incidence of cancer has not changed in recent years, and, in our context, the number of PET exams performed at our centre has not significantly changed in 2020 compared with 2019 as well as the planning of staging FDG PET/CT exams, which are generally performed within 7 days of receiving the request form. We have only recorded a slight reduction in PET/CT requests for patients on treatment due to cancellation or postponement of the examination with a consequent greater availability to perform examinations for staging or restaging purposes. Given that the incidence of cancer has not significantly changed in recent years, the increase in the number of FDG PET/CT requests for staging purposes immediately after the national lockdown is most likely due to the delay of cancer diagnosis in many patients due to the restrictions imposed by the government and hospital saturation due to COVID patients. Delays in cancer diagnosis led to more patients being diagnosed at a more advanced stage of their disease, as demonstrated by our study. This means that these patients might require more complex treatments than otherwise needed and that more deaths result from cancer. The exact extent of the effects on survival and healthcare costs will only become evident in the next few years. After the first peak of the pandemic, forecasts on the impact of these delays on cancer diagnosis and patient survival were provided. The severity of the indirect effects of

the COVID-19 pandemic was clear in November 2020 when a 4-week treatment delay was reported to be associated with a 6 to 17% increased risk of death depending on cancer type. Delays of up to 12 weeks increase this risk further [33–36]. However, the challenge is to prevent that new waves of the pandemic limit access to cancer diagnosis and treatment, by constructing a health system which adequately responds to the needs of these advanced stage patients both during and shortly after the pandemic. We hope that the detrimental impact of the COVID-19 pandemic on cancer patients could be mitigated with the support of all stakeholders in cancer diagnosis, treatment, and health planning processes. This study has some limitations. First, this is a retrospective study with its intrinsic limitations, which, however, indirectly allowed us to take a snapshot of real events related to this emergency. Secondly, we focused on patients with FDG-avid tumours excluding other malignancies such as prostate cancer or neuroendocrine tumours that are usually studied with radiopharmaceuticals other than FDG. Nevertheless, FDG is the radiopharmaceutical most frequently used for PET, and FDG-avid tumours are the most aggressive cancer types for which a delay in diagnosis and treatment initiation could have the worst consequences on patients' outcome [37]. In addition, considering the subset of patients studied (with cancers at staging), it is unlikely that the results are biased by the inclusion of data from the summer months of 2019, which were vacation months. Conversely, the obtained results (rates in particular) are likely due to the saturated hospitality capacity during the COVID-19 outbreak. Finally, we did not find any statistically significant difference in myeloma and head and neck tumours most likely due to the low sample size. Further, more complex, studies addressed to evaluate patient outcome, survival, and healthcare costs are desirable to confirm our results.

Conclusion

The COVID-19 pandemic has had a huge and negative impact on the diagnosis and initiation of cancer treatment. Overall, the rate of oncological patients with advanced disease stage at time of FDG PET/CT staging increased 1.5-fold in 2020 compared with 2019 with a twofold increase of patients with nodal involvement and distant metastases. Targeted health interventions are needed to mitigate the expected impact of the COVID-19 pandemic on the outcome of cancer patients.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00259-021-05629-0>.

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Author contribution All authors contributed to the study conception and design. Material preparation and data collection were performed by Carmelo Caldarella, Fabrizio Cocciolillo, Silvia Taralli, Margherita Lorusso, Valentina Scolozzi, Daniele Antonio Pizzuto, and Lucia Leccisotti. Data analysis was performed in the Gemelli Science and Technology Park (GSTeP), the Bioinformatics Core Facility Research, by Davide Guido, Fernando Palluzzi, and Luciano Giacò. The first draft of the manuscript was written by Carmelo Caldarella and Lucia Leccisotti, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval This retrospective observational study involving human participants was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS-Università Cattolica del Sacro Cuore approved this study (Date 15.4.2021/No. 4024).

Conflict of interest The authors declare no competing interests.

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