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Change in cancer diagnosis during the COVID-19 pandemic: Trends estimated from FDG-PET/CT

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Abstract: The aim of this study is to clarify changes in the circumstances of cancer diagnoses during the COVID-19 pandemic in Tokyo, Japan, estimated from [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) -positron emission tomography/computed tomography (PET/CT) for cancer patients. Cancer diagnosis in pandemic status (PANS) was evaluated by retrospective review of the findings of FDG-PET/CT examinations performed between 11 March 2020 and 28 December 2021 for initial staging and restaging for malignancy. Evaluation of cancer diagnosis in pre-pandemic status (pPANS) was conducted similarly in FDG-PET/CT examinations performed between 4 January 2018 and 10 March 2020. Of these, patients with malignant lymphoma (ML), lung cancer, esophageal cancer, and colorectal cancer who had a pathologically proven diagnosis or clinical diagnosis following therapy of the disease were selected for analysis. Initial cancer staging was determined by the diagnostic report of FDG-PET/CT. Change in cancer stage and in the number of FDG-PET/CT examinations performed was evaluated between pPANS and PANS, and according to term of the pandemic and vaccination status. The COVID-19 epidemic influenced the number of cancer patients who underwent FDG-PET/CT. There was a marked decrease in the number of cancer patients receiving FDG-PET/CT in Terms 1-3 (March 2020 to February 2021), but it recovered in Terms 4-6 (March 2021 to December 2021). There was no significant difference between PANS and pPANS in terms of the initial stage of cancer, but Stage IV ML and Stage II esophageal cancer were more frequent in PANS. Initial staging of ML, lung cancer, and esophageal cancer revealed more advanced cancer stages in Terms 4-6 compared with Terms 1-3. The number of patients receiving FDG-PET/CT in Tokyo was influenced by the COVID-19 epidemic. Staging based on FDG-PET/CT shifted to more advanced cancer stage during the pandemic compared with pre-pandemic.

***Keywords*:** COVID-19, pandemic, FDG-PET/CT, cancer stage, vaccination, Japan

Introduction

The novel coronavirus disease 2019 (COVID-19) outbreak spread across the world within a few months of the first report of its identification as severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in January 2020 (*1*). On 11 March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic (*2*). In Tokyo, Japan, the first emergency declaration due to the COVID-19 outbreak was announced on 7 April 2020, and it had totally reached 4 times by the end of 2021.

The National Center for Global Health and Medicine (NCGM) is one of six National Centers in Japan with specific responsibility for management of infectious disease outbreaks. Since the first COVID-19 patient was confirmed in Japan in January 2020, the NCGM Center Hospital in Tokyo expanded its capacity for COVID-19 patients according to patient load, with peak capacity of 70 beds, including 8 intensive care unit beds (*3*). However, the hospital was forced to set priorities for the care of non-COVID-19 patients based on Business Continuity Planning (BCP) for dealing with the emergency situation. Based on BCP, hospitals temporally enacted restrictions on daily medical care systems and suspension of medical checkups including cancer screening. Social trends toward refraining from hospital consultation and regularly scheduled hospital or clinic visits occurred due to restrictions in the general medical care system and people's anxiety about contracting COVID-19. During the first wave of the pandemic in the United Kingdom (March - August 2020), an estimated 45% of people with potential cancer symptoms did not contact their doctor (*4,5*). Rodriguez *et al.* reported that COVID-19 had a marked impact on cancer care, with 46% of patients experiencing a change in care,

including treatment delay in 33% of patients and change of care location in 12%. The average duration of cancer-related care delays was greater than 4 weeks in 71.4% of clinic visits, 79.3% of laboratory testing or blood work, and 80.0% of imaging examinations (*6*). In the state of Victoria, Australia, approximately 2,500 cancer diagnoses were estimated to have been missed during the first 6 months of the pandemic (*7*). In Japan, the number of patients diagnosed with cancer was reported to have decreased after the pandemic (*8-10*), raising strong concern that a large number of patients would present with more advanced cancer in the future (*4*).

The glucose analog [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) is a molecular imaging probe used to evaluate tissue glucose utilization and glucose metabolism. FDG-positron emission tomography/computed tomography (PET/CT) has utility in the staging, restaging, and assessment of therapeutic effects in malignancy, and is used in the management of patients with malignancy (*11*). PET/CT is also used as a part of the cancer screening program in Japan (*12*). Nuclear medicine departments have established effective procedures for patients and staff flow when facing known, suspected, and incidentally detected COVID-19 patients. These measures enabled transmission of the virus to be controlled while continuing to provide essential and critical services (*13,14*). With regard to nuclear medicine examinations including FDG-PET/CT, our department checked patients for clinical manifestations before the examination, and carefully surveyed the chest CT findings and noted any abnormal FDG uptake related to COVID-19, and alerted immediately to a doctor in charge if COVID-19 infection was suspected.

Under these conditions, it was unclear whether changes to medical care made in response to the COVID-19 pandemic had affected new cancer diagnoses and follow up in cancer patients. The aim of this retrospective study was to clarify change in the circumstances of cancer diagnosis during the COVID-19 pandemic, estimated based on FDG-PET/CT examinations performed in cancer patients.

Patients and Methods

Subjects

All study protocols in this retrospective observational study with waiver of patient informed consent were approved by our institutional review board (NCGM-S-004423-00). In evaluation of pandemic status (PANS), we surveyed FDG-PET/CT examinations performed between 11 March 2020 and 28 December 2021 (21.7 months) in patients aged ≥ 20 years, and selected those who had undergone FDG-PET/CT for initial staging and restaging (for the diagnosis of recurrence or new metastasis, or assessment of therapeutic effect in cases of malignant lymphoma [ML] only) of malignancy. In evaluation of pre-pandemic status (pPANS), we surveyed FDG-PET/CT examinations performed between 4 January and 10 March 2020 (26.3 months) in patients aged ≥ 20 years, and selected those who had undergone FDG-PET/CT for initial staging and restaging of malignancy, as described for PANS. With consideration to the number of available FDG-PET/CT examinations for each malignancy, we selected patients with ML, lung cancer, esophageal cancer, or colorectal cancer (excluding appendix and anal cancer) who had a pathologically proven diagnosis or a clinical diagnosis following therapy. Excluded cases were patients who underwent FDG-PET/CT for initial staging with no further definitive diagnosis of malignancy, and those with possible early-stage cancer observed clinically but without any definitive diagnosis.

Cancer stage based on FDG-PET/CT

Initial cancer stage was determined by the FDG-PET/CT diagnostic report made by board of nuclear medicine and diagnostic radiology, according to the 8th edition of the UICC-TNM classification for lung, esophageal, and colon cancer (*15*), and with the Lugano classification for malignant lymphoma (*16*). If no malignant lesion was identified on FDG-PET/CT, the patient was not included in this study even for lesions that were finally proven as malignant. Diagnostic report on brain MRI performed in the process of lung cancer staging was referred for checking the brain metastasis which could not identified by FDG-PET/CT.

Reference data and definitions

The number of cases of COVID-19 in Tokyo, Japan was obtained from the website established by the Tokyo Metropolitan Government (*17*). The trend of COVID-19 patients in Tokyo is presented in Figure 1A. After declaration of the COVID-19 outbreak as a global

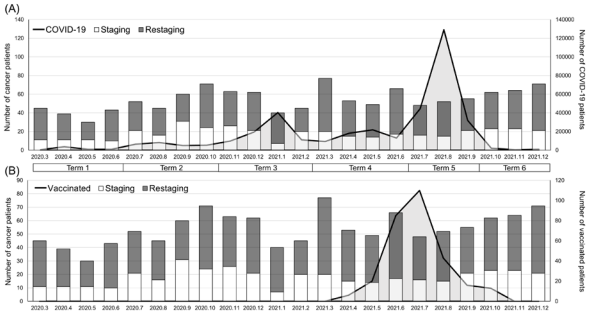

Figure 1. The trend of COVID-19 patients, cancer patients undergone FDG-PET/CT and status of COVID-19 vaccination. (A) the trend of COVID-19 patients in Tokyo and cancer patients undergone FDG-PET/CT; **(B)** COVID-19 vaccination status and cancer patients undergone FDG-PET/CT.

pandemic, 5 waves of COVID-19 occurred in Tokyo. We defined six PANS terms according to outbreak wave number as follows: Term 1 (related to the 1st wave), 11 March 2020 to 30 June 2020; Term 2 (related to 2nd wave), 1 July 2020 to 31 October 2020; Term 3 (related to the 3rd wave), 1 November 2020 to 28 February 2021; Term 4 (related to the 4th wave), 1 March 2021 to 30 June 2021; Term 5 (related to the 5th wave), 1 July 2021 to 30 September 2021; and Term 6 (sharp decline in the number of COVID-19 cases after the 5th wave), 1 October 2021 to 28 December 2021.

COVID-19 vaccination

From 1 June 2021, we interviewed the vaccination status from all patients who underwent FDG-PET/CT examination in our department (date of 1st and 2nd vaccinations and side of arm for injection) because COVID-19 vaccination can affect specific findings of FDG uptake and thus influence image interpretation (*18*). For this reason, we advised physicians and patients of the recommendation to wait at least six weeks after vaccination before having FDG-PET/CT examination, but scheduling of FDG-PET/CT was ultimately decided based on the disease status of the patient. COVID-19 vaccination status according to type of malignancy in patients who underwent FDG-PET/CT is shown in Figure 1B.

Results

Cancer patients who underwent FDG-PET/CT and COVID-19 patients in Tokyo

The number of cancer patients who visited our hospital for receiving FDG-PET/CT decreased during each peak of COVID-19 cases in Tokyo (May 2020, August 2020, January to February 2021, July to September 2021) and increased when the case numbers dropped (June 2020, September to October 2020, March 2021, October to December 2021). The number of patients who received FDG-PET/CT for initial staging of cancer increased between the peaks of Terms 2 and 3 and became constant during Terms 4 to 6. The number of patients who received FDG-PET/CT for restaging of cancer increased temporarily when the case numbers dropped and became almost constant during other periods (Figure 1A).

Cancer patients receiving FDG-PET/CT and vaccination status

Among the present patient cohort, vaccination against COVID-19 began in March 2021 and peaked in July 2021 (Figure 1B). Of patients who underwent FDG-PET/CT in March 2021 to December 2021, 47.3% (243/514) had been vaccinated at least one time: 44.1% (82/186) of those for initial staging and 49.1% (161/328) of those for restaging. The duration between the last vaccination and FDG-PET/CT showed several peaks in patient numbers for restaging, but there was no remarkable peak in those for initial staging (Table 1 and Figure 2). Although recommended to avoid FDG-PET/CT for at least 6 weeks after vaccination, it was apparent that patient status had been given priority in the decision whether or not to perform FDG-PET/CT.

Table 1. Duration between FDG-PET/CT and last COVID-19 vaccination

Duration (days)	Staging (n = 82)	Restaging (n = 161)	All (n = 243)
Average (± SD)	84 ± 57	75 ± 57	78 ± 57
Range	2 - 204	4 - 243	2 - 243
Median	83.5	63	69

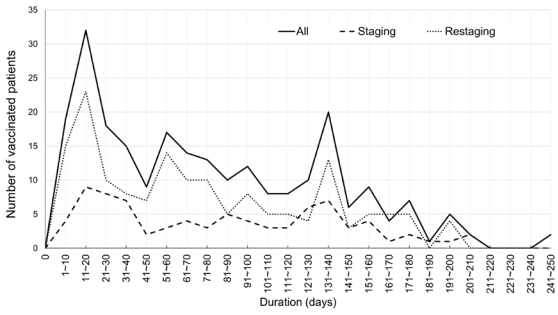

Figure 2. Duration between FDG-PET/CT examination and COVID-19 vaccination.

Malignant lymphoma

The average age of patients with ML who underwent FDG-PET/CT showed no change between pPANS (65 ± 15) and PANS (66 ± 14). The number of patients receiving FDG-PET/CT examinations per month was higher in PANS (20.7 patients/month) than in pPANS (11.7 patients/month) in these patients (Table 2). The number of FDG-PET/CT examinations per month was slightly higher in Terms 4-6 (21.2 patients/month) than in Terms 1-3 (20.3 patients/month) and dropped temporarily in Term 5 (Table 2, Figure 3A). The ratio of purpose for FDG-PET/CT examination was shifted from initial staging to restaging in PANS (pPANS: staging 23.3%, restaging 76.7%, PANS: staging 19.2%, restaging 80.8%) (Table 2). The rates of Stage I and Stage IV disease was higher in PANS (Stage I: 32.6%, Stage IV: 37.2%) than in pPANS (Stage I: 27.8%, Stage IV: 25.0%), and the initial cancer stage was more advanced in Terms 4-6 (Stage I: 28.6%, II: 11.9%, III: 19.0%, IV: 40.5%) than in Terms 1-3 (Stage I: 36.4%, II: 11.3%, III: 18.2%, IV: 34.1%). No specific trend in cancer stage was observed in patients with ML, but Stage IV disease was constantly diagnosed in PANS (Figure 4A).

Table 2. Characteristics of patients with malignant lymphoma receiving FDG-PET/CT

Variables	PANS			pPANS		
Role of examination	Number	Ratio (%)		Number	Ratio (%)	
Staging	86 (44/42)	19.2 (18.6/19.8)		72	23.3	
Restaging	363 (193/170)	80.8 (81.4/80.2)		237	76.7	
Total	449 (237/212)			309		
Number per month	20.7 (20.3/21.2)			11.7		
Cancer stage	Number	Ratio (%)		Number	Ratio (%)	
1	28 (16/12)	32.6 (36.4/28.6)		20	27.8	
2	10 (5/5)	11.6 (11.3/11.9)		15	20.8	
3	16 (8/8)	18.6 (18.2/19.0)		19	26.4	
4	32 (15/17)	37.2 (34.1/40.5)		18	25.0	
Age	Staging	Restaging	All	Staging	Restaging	All
Average (± SD)	66 ± 16	66 ± 14	66 ± 14	66 ± 16	64 ± 15	65 ± 15
Range	30 - 93	20 - 93	20 - 92	20 - 86	20 - 91	20 - 91
Median	70.5	69	69	68.5	68	68

Data in parenthesis represent the situation of Term 1-3/Term 4-6.

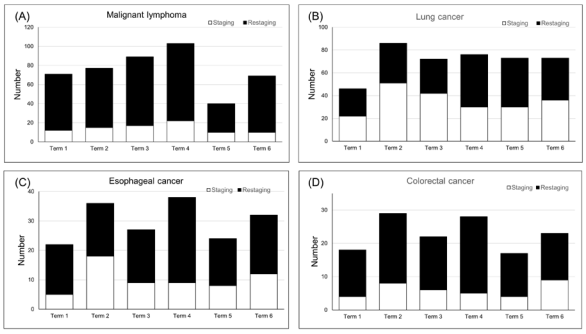

Figure 3. The number of cancer patients undergone FDG-PET/CT for staging and restaging in 4 types of cancers in each term. (A) malignant lymphoma, **(B)** lung cancer, **(C)** esophageal cancer, **(D)** colorectal cancer.

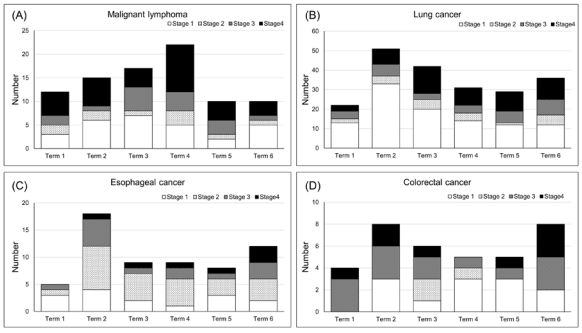

Figure 4. Cancer staging by FDG-PET/CT in 4 types of cancers in each term. (A) malignant lymphoma, **(B)** lung cancer, **(C)** esophageal cancer, **(D)** colorectal cancer.

Lung cancer

There was no change between pPANS (70 ± 11) and PANS (72 ± 11) in terms of average age in the patients with lung cancer, and the number of FDG-PET/CT examinations per month was almost the same between pPANS (19.4 patients/month) and PANS (19.6 patients/month). The number of FDG-PET/CT examinations per month was higher in Terms 4-6 (22.2 patients/month) than in Terms 1-3 (17.4 patients/month). The ratio of purpose for FDG-PET/CT was almost the same between pPANS and PANS (pPANS: staging 50.7%, restaging 49.3%, PANS: staging 49.5%, restaging 50.5%). Compared with Terms 1-3, more patients underwent FDG-PET/CT for restaging than for initial staging in Terms 4-6 (Table 3, Figure 3B). In PANS, cancer stage shifted to an earlier stage, but the rates of Stage I to Stage IV disease did not change. Cancer stage was more advanced in Terms 4-6 (Stage I: 39.6%, II: 10.4%, III: 18.8%, IV: 31.3%) than in Terms 1-3 (Stage I: 57.4%, II: 9.6%, III: 11.3%, IV: 21.4%). The number of Stage I cancers increased temporarily in Term 2, and advanced cancer stage was more common in later terms (Figure 4B). With referring to the result on contrast-enhanced brain MRI, FDG-PET/CT could not identify 9 cases of brain metastases in pPANS and 10 cases of them in PANS. Based on this result, stage IV cancer was underestimated in two cases (both stage III by FDG-PET/CT) in PANS, but no case in pPANS.

Esophageal cancer

Mean age of the patients with esophageal cancer was slightly higher in PANS (70 ± 9) than in pPANS (68 ± 10). The number of FDG-PET/CT examinations per month was slightly lower in PANS (pPANS, 8.9 patients/month; PANS, 8.3 patients/month), and the number of patients was higher in Terms 4-6 (9.5 patients/month) than in Terms 1-3 (7.3 patients/month) (Table 4). The number of FDG-PET/CT examinations performed for initial staging was greatest in Term 2, followed by Term 6 (Figure 3C). The ratio of purpose of FDG-PET/CT were similar between pPANS and PANS (pPANS: staging 30.5%, restaging 69.5%, PANS: staging 33.9%,

Table 3. Characteristics of patients with lung cancer receiving FDG-PET/CT

Variables	PANS			pPANS		
Role of examination	Number	Ratio (%)		Number	Ratio (%)	
Staging	211 (115/96)	49.5 (56.4/43.2)		259	50.7	
Restaging	215 (89/126)	50.5 (43.6/56.8)		252	49.3	
Total	426 (204/222)			511		
Number per month	19.6 (17.4/22.2)			19.4		
Cancer stage	Number	Ratio (%)		Number	Ratio (%)	
1	104 (66/38)	49.3 (57.4/39.6)		116	44.8	
2	21 (11/10)	10.0 (9.6/10.4)		33	12.7	
3	31 (13/18)	14.7 (11.3/18.8)		45	17.4	
4	55 (25/30)	26.1 (21.4/31.3)		65	25.1	
Age	Staging	Restaging	All	Staging	Restaging	All
Average (± SD)	72 ± 11	71 ± 11	72 ± 11	71 ± 11	70 ± 11	70 ± 11
Range	38 - 94	34 - 95	34 - 95	31 - 92	37 - 90	31 - 92
Median	74	72	73	72	71	71

Data in parenthesis represent the situation of Term 1-3/Term 4-6.

Table 4. Characteristics of patients with esophagus cancer receiving FDG-PET/CT

Variables	PANS			pPANS		
Role of examination	Number	Ratio (%)		Number	Ratio (%)	
Staging	61 (32/29)	33.9 (37.6/30.9)		71	30.5	
Restaging	118 (53/65)	66.1 (62.4/69.1)		162	69.5	
Total	180 (85/94)			233		
Number per month	8.3 (7.3/9.5)			8.9		
Cancer stage	Number	Ratio (%)		Number	Ratio (%)	
1	15 (9/6)	24.6 (28.1/20.7)		20	28.2	
2	26 (14/12)	42.6 (43.8/41.4)		23	32.4	
3	13 (7/6)	21.3 (21.9/20.7)		14	19.7	
4	7 (2/5)	11.5 (6.3/17.2)		14	19.7	
Age	Staging	Restaging	All	Staging	Restaging	All
Average (± SD)	72 ± 8	69 ± 9	70 ± 9	68 ± 10	67 ± 10	68 ± 10
Range	56 - 91	43 - 92	43 - 92	31 - 88	38 - 87	31 - 88
Median	73	70	71	70	68.5	69

Data in parenthesis represent the situation of Term 1-3/Term 4-6.

restaging 66.1%), but compared with Terms 1-3 (staging 37.6%, restaging 62.4%), there was a slight shift from initial staging to restaging in Terms 4-6 (staging 30.9%, restaging 69.1%). The rates of Stage I and IV cancer were lower and that of Stage II cancer was higher in PANS (Stage I: 24.6%, II: 42.6%, III: 21.3%, IV: 11.5%) than in pPANS (Stage I: 28.2%, II: 32.4%, III: 19.7%, IV: 19.7%) (Table 4). Compared with Terms 1-3 (Stage I: 28.1%, II: 43.8%, III: 21.3%, IV: 6.3%), cancer stage was more advanced in Terms 4-6 (Stage I: 20.7%, II: 41.4%, III: 20.7%, IV: 17.2%) (Figure 4C). In Terms 4-6, the rate of Stage IV cancer (0.50 patients/month) was higher than in Terms 1-3 (0.17 patients/month) and almost equal to that in pPANS (0.53 patients/month).

Colorectal cancer

The average age of patients with colorectal cancer who underwent FDG-PET/CT showed no change between pPANS (63 ± 13) and PANS (62 ± 14). In these patients, the number of FDG-PET/CT examinations per month was slightly higher in PANS than in pPANS (pPANS, 5.8 patients/month; PANS, 6.3 patients/month), and was higher in Terms 4-6 (6.8 patients/month) than in Terms 1-3 (5.9 patients/month) (Table 5). The number of FDG-PET/CT examinations performed for initial staging was greatest in Term 6, followed by Term 2 (Figure 3D). Compared with pPANS, more examinations were performed for the purpose of initial staging in PANS (pPANS: staging 20.4%, restaging 79.6%, PANS: staging 26.9%, restaging 73.1%), and there was no difference between Terms 4-6 (staging 26.5%, restaging 73.5) and Terms 1-3 (staging 26.1%, restaging 73.9) (Table 5, Figure 3D). The stage of colorectal cancer shifted to an earlier stage in PANS (pPANS; Stage I: 16.1%, II: 6.5%, III: 41.9%, IV: 35.5%, PANS; Stage I: 33.3%, II: 8.3%,

Table 5. Characteristics of patients with colorectal cancer receiving FDG-PET/CT

Variables	PANS			pPANS		
Role of examination	Number	Ratio (%)		Number	Ratio (%)	
Staging	36 (18/18)	26.9 (26.1/26.5)		31	20.4	
Restaging	101 (51/50)	73.1 (73.9/73.5)		121	79.6	
Total	137 (69/68)			152		
Number per month	6.3 (5.9/6.8)			5.8		
Cancer stage	Number	Ratio (%)		Number	Ratio (%)	
1	12 (4/8)	33.3 (22.2/44.4)		5	16.1	
2	3 (2/1)	8.3 (11.1/5.6)		2	6.5	
3	13 (8/5)	36.1 (44.4/27.8)		13	41.9	
4	8 (4/4)	22.2 (22.2/22.2)		11	35.5	
Age	Staging	Restaging	All	Staging	Restaging	All
Average (± SD)	65 ± 14	61 ± 14	62 ± 14	59 ± 14	65 ± 13	63 ± 13
Range	39 - 88	29 - 88	29 - 88	29 - 79	29 - 89	29 - 89
Median	68.5	62	63	60	66	65

Data in parenthesis represent the situation of Term 1-3/Term 4-6.

III: 36.1%, IV: 22.2%). Cancer stage shifted to an earlier stage in Terms 4-6 (Stage I: 44.4%, II: 5.6%, III: 27.8%, IV: 22.2%) compared with Terms 1-3 (Stage I: 22.2%, II: 11.1%, III: 44.4%, IV: 22.2%), but the highest number of advanced stage cancers were in Term 6 (Figure 4D).

Discussion

This study evaluated change in cancer diagnosis by FDG-PET/CT during the COVID-19 pandemic compared with the pre-pandemic status. The number of patients who underwent FDG-PET/CT was influenced by the COVID-19 epidemic in Tokyo. There was a prominent decrease in cancer patients underwent FDG-PET/CT in Terms 1-3 but the numbers recovered in Terms 4-6. Our results showed no significant difference between PANS and pPANS regarding the number of examinations performed for initial cancer staging, but the rates of Stage IV disease of ML and Stage II of esophageal cancer were increased in PANS. The initial stage of ML, lung cancer, and esophageal cancer shifted to a more advanced stage in Terms 4-6 compared with Terms 1-3.

In patients who underwent FDG-PET/CT for initial staging, COVID-19 had a greater effect in Terms 1-3 than in Terms 4-6. The number of patients who underwent FDG-PET/CT for restaging showed a temporary increase after the peak of COVID-19 had passed. This finding indicates that the COVID-19 epidemic did indeed impact cancer patients, but to a lesser degree in Terms 4-6, when one year had passed after declaration of the COVID-19 pandemic. It is noteworthy that the number of patients who underwent FDG-PET/CT gradually kept increased in the time of the large peak in COVID-19 cases in August 2021. When the peak vaccination rate in July 2021 is taken into account, it is possible that vaccination may have influenced patients' psychological condition. Although the average period between vaccination and FDG-PET/CT was approximately 80 days, the peak timing was 11-20 days after vaccination. Our department recommended waiting at least 6 weeks after vaccination before scheduling an FDG-PET/CT examination (*18*), but the patient's condition and treatment planning was given priority. However, over half of the patients were not vaccinated at the time of the FDG-PET/CT examination. Patients with cancer and cardiovascular disease are at high risk for worse clinical outcomes in COVID-19 infection (*19*), and vaccination against COVID-19 helps prevent serious complications (*20*). The attitude of the present patients toward vaccination is unclear, and the recommendation timing of vaccination in cancer patients appears to be an ongoing issue.

In Japan, the diagnosis of five types of cancer (gastric, colon, lung, breast, and cervical cancer) were 9.2% lower in 2020 than in 2019 (*8*). In 2020, the number of newly diagnosed cancers was reduced by 13.4% in gastric cancer, 10.2% in colon cancer, 8.2% in breast cancer, 6.4% in lung cancer and 4.8% in cervical cancer, compared with those diagnosed in 2019 (*8*). In US and the UK, a significant decline in the number of encounters with cancer had been reported for April 2020 compared with 2019. Lung (-39.1%), colorectal (-39.9%), and hematologic (-39.1%) cancer cohorts showed smaller decreases in size compared with decreases in cohort size for breast cancer (-47.7%), prostate cancer (-49.1%), and melanoma (-51.8%) (*21*), which suggests that the impact of the COVID-19 pandemic might have differed according to the type of cancer.

In the present study, the number of FDG-PET/CT examinations increased between Terms 1 and 4 in ML patients, but this trend was not observed in the other three cancer types. There is no specific screening program for ML and patients are generally referred to the hospital after the emergence of clinical symptoms such as continuous fever and lymph node swelling. As

early diagnosis and treatment is essential in patients with aggressive disease, hospitals should consider retaining capacity to accept these patients and reflect it to BCP. The other three types of cancer have specific screening programs: low-dose chest CT for lung cancer screening, upper endoscopy for esophageal cancer, and lower endoscopy and fecal occult blood testing for colorectal cancer. Many major cancer organizations have recommended delaying screening studies such as screening mammograms, colonoscopy, and surveillance for lung cancer during the COVID-19 pandemic (*22,23*). However, delay in the diagnosis of rapidly growing malignancies such as breast and lung cancer carry the risk of causing adverse outcomes (*24,25*), whereas suspension of screening for slow-growing malignancies such as prostate cancer and cervical cancer are considered to have a minimal effect on outcomes. (*25,26*).

According to the Japan Cancer Society, 30.5% fewer people underwent cancer screening for five types of cancer in 2020 compared with 2019 (*27*). The screening rate had recovered by the first half of 2021, but was still 17.4% lower than in 2019 (*28*). Therefore, it is possible that the number of FDG-PET/CT examinations performed for initial cancer staging could have been affected by the reduction in cancer screenings, which decreased the opportunity to detect cancer in the early stages.

Maringe *et al*. estimated the impact of delays in diagnosis on cancer survival outcomes in breast, colorectal, esophageal, and lung cancer. Compared with the pre-pandemic status, the estimated increase of deaths in the pandemic status was 7.9-9.6% for breast cancer, 15.3-16.6% for colorectal cancer, 4.8-5.3% for lung cancer, and 5.8-6.0% for esophageal cancer, up to year 5 after diagnosis (*29*). It is known that delays in therapy for cancer have a significant impact on survival (*30*). Delays of 3 or 6 months in surgery for incident cancers have been shown to reduce life-years gained by 19% and 43%, respectively (*31*). As another critical issue, even a 3-month delay in diagnosis and initiation of treatment due to the COVID-19 pandemic was shown to result in excess healthcare costs (*32*).

The present results showed no significant difference between PANS and pPANS in terms of the number of FDG-PET/CT examinations performed for initial staging, however the rate of detection of Stage IV disease in ML and Stage II disease in esophageal cancer were higher in PANS than in pPANS.

The initial stage of ML, lung cancer, and esophageal cancers shifted to a more advanced stage in Terms 4-6 compared with Terms 1-3. These results may indicate that the shift to a more advanced stage first began in 2021, and occurred earlier in ML due to the aggressiveness of the disease. This trend should be monitored to understand of the actual impact of the COVID-19 pandemic on patients with cancer.

It is known that FDG-PET/CT has limitations in assessment of lesions that have high background physiologic FDG uptake, which led to brain metastasis being missed by FDG-PET/CT in several of the present cases, and have caused underestimation of cancer staging. Small lesions (< 10 mm) can be missed by FDG-PET/CT due to the limited resolution of PET. FDG-PET/CT has limitations in detecting bone marrow invasion in ML, which might have caused underestimation of staging in ML.

The limitations of this study include its retrospective design and that it was conducted at a single institution. Seasonal variations in the number cancer patients underwent FDG-PET/CT were not taken into account. Hospitals in Japan have played different roles during the COVID-19 pandemic, and the trends in cancer patients may differ among hospitals. To understand the influence of the COVID-19 pandemic on cancer patients, a large multicenter study is warranted.

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