Cancer Diagnostic Delay in Northern and Central Italy During the 2020 Lockdown Due to the Coronavirus Disease 2019 Pandemic

Assessment of the Magnitude of the Problem and Proposals for Corrective Actions

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ABSTRACT

Objectives: *We performed data collection concerning the coronavirus disease 2019 (COVID-19) pandemic-related delay in the diagnosis of cancers to individuate proper corrective procedures.*

Methods: *A comparison was made among the number of first pathologic diagnoses of malignancy made from weeks 11 to 20 of 2018, 2019, and 2020 at seven anatomic pathology units serving secondary care hospitals in northern-central Italy.*

Results: *Cancer diagnoses fell in 2020 by 44.9% compared with the average number recorded in 2018 and 2019. Melanoma and nonmelanoma skin cancer represented 56.7% of all missing diagnoses. The diagnostic decrease in colorectal (–46.6%), prostate (–45%), and bladder (–43.6%) cancer was the most relevant among internal malignancies; for prostate, however, high-grade tumors were only moderately affected (–21.7%).*

Conclusions: *Diagnosis of cutaneous malignancies was mostly affected by the lockdown; among internal malignancies, corrective actions were mostly needed for colorectal cancer and invasive bladder cancer.*

Key Points

- The coronavirus disease 2019 (COVID-19) pandemic induced a delay in the cellular pathologic diagnosis of major cancers.
- The number of first diagnoses of malignancy made in the lockdown period compared with the same period of previous years may help identify the COVID-19–related cancer diagnostic delay.
- At seven secondary care hospital networks in northern and central Italy, the first diagnosis of cutaneous malignancies was most affected by the lockdown.

The coronavirus disease 2019 (COVID-19) pandemic started in Italy with 16 confirmed cases in Lombardy on February 21, 2020; on March 9, 2020 (week 11 of the year), the Italian prime minister imposed a national lockdown; limitations mostly ran up to May 17, 2020 (week 20). The pandemic increased the stress on the regional health care systems in northern and central Italy, mainly in their emergency and intensive care units. Although not directly under pressure by the pandemic, the Italian anatomic pathology units were forced to adopt standard operative procedures aimed at minimizing the risks related to autopsy procedures and cellular sample handling.[1,2]

The risk of disease spread inside crowded hospitals induced the American Society of Clinical Oncology to

recommend that "any clinic visits that can be postponed without risk to the patient should be postponed."[3] The COVID-19 pandemic also affected the compliance of patients toward scheduled but deferrable diagnostic and therapeutic procedures.[4] Mass screening programs for breast, colorectal, and cervical cancer were interrupted.

A standards-based audit was recently performed with the aim of evaluating the pandemic-related delay in the pathologic diagnosis of cancers by comparing the number first diagnoses of tumors finalized during weeks 11 to 20 of 2020, 2019, and 2018 at a pathologic anatomy unit serving a secondary care hospital network.[5] The present study collected similar data from seven secondary care hospital networks, all highly affected by the COVID-19 pandemic.[6] The delays in the clinical procedures finalized to achieve a pathologic diagnosis were thus evaluated over a broad geographic area. The proposed corrective procedures potentially implied a multi-institutional strategic positioning to tackle the COVID-19–related backlog in cancer care.

Materials and Methods

The Marche Regional Ethical Committee (Ancona, Italy) approved the present study as part of the regional Quality Control Program in Cancer Care (QCPCC). The goal of the QCPCC is to develop prioritizing and funding strategies for evidence-based cancer care with proper performance targets and outcome measures. The decrease in the number of pathologic diagnoses of malignancy during the lockdown period, assumed to represent a diagnostic delay of cancer, was conceived as the basic criterion to develop prioritizing strategies in cancer care during the COVID-19 era.

The study involved seven anatomic pathology units, all serving secondary care hospital networks with a hub-spoke organization[7] from seven different regions in northern and central Italy. ❙Table 1❙ shows the main characteristics of the participating institutions, all heavily affected by the COVID-19 pandemic.[4] Overall, the anatomic pathology units involved in the present study serve a 6,548-mi^2 territory with about 2,270,000 inhabitants (about one twelfth of the whole population of the seven regions).

By means of the laboratory information management systems of the involved units, the number of all first cytopathologic and histopathologic diagnoses of primary malignancy and metastatic disease (from a known/unknown) made in weeks 11 to 20 of 2020 and 2018 to 2019 (given as an average) was retrieved. There was a focus on the most common cancers affecting the Italian population (breast, prostate, lung, colorectal, bladder, stomach, non-Hodgkin lymphoma, liver, and skin-melanoma) according to the Global Cancer Observatory (GCO) 2018.[8] Data regarding nonmelanoma skin cancer (NMSC), by definition not included in the GCO 2018 data, were also collected because NMSC is by far the most common group of human malignancies.[9] Histopathologic prognostic

❙Table 1❙
Characteristics of the Secondary Care Hospital Networks Involved in the Study

Region	Hospital Network	Pathology Hub	Territory Served	Facilities	Total No. of Beds
Marche	Area Vasta n. 3 Azienda Sanitaria Unica Regionale Marche	Macerata General Hospital—Macerata	Province of Macerata 1,073 mi^2 300,000 inhabitants	3 secondary care centers 1 primary care center Outpatient network	736
Emilia Romagna	Azienda Unità Sanitaria Locale Romagna	"G. B. Morgagni – L. Pierantoni" Hospital—Forlì	Province of Forlì-Cesena 918 mi^2 188,000 inhabitants	1 secondary care center Outpatient network	461
Trentino-Alto Adige	Azienda Provinciale per i Servizi Sanitari di Trento	"Santa Chiara" Hospital—Trento	Province of Trento 2,397 mi^2 541,000 inhabitants	5 secondary care centers 7 primary care centers Outpatient network	1,561
Lumbardy	Azienda Socio-Sanitaria Locale "Valle Olona"	Busto Arsizio Hospital—Busto Arsizio	Southern Province of Varese 278 mi^2 510,000 inhabitants	1 secondary care center 3 primary care centers Outpatient network	1,184
Veneto	Azienda Unità Locale Socio-Sanitaria 5 Polesana	"Santa Maria della Misericordia" Hospital—Rovigo	Province of Rovigo 702 mi^2 241,000 inhabitants	2 secondary care centers 1 primary care center Outpatient network	738
Piedmont	Azienda Sanitaria Locale Asti	"Cardinal Massaia" Hospital—Asti	Province of Asti 583 mi^2 215,000 inhabitants	1 secondary care center Outpatient network	527
Liguria	Azienda Sanitaria Locale 2 della Liguria	"San Paolo" Hospital—Savona	Province of Savona 597 mi^2 275,000 inhabitants	2 secondary care centers 2 primary care centers Outpatient network	1,012

indices were studied for some internal malignancies with the greatest diagnostic decrease in 2020.

Results

The number of new, or first metastatic, diagnoses of malignancy recorded in the 10-week observation period was 2,751 in 2020 and, on average, 4,991.5 in 2018 to 2019, representing a decrease in 2020 of 44.9%. ❙Figure 1❙ shows the week-to-week trend in the number of diagnoses: the lockdown phase started in week 11 with 420 diagnoses of malignancy, a number that was 26.6% lower than those made in the same week of 2018 to 2019; the nadir of the curve was reached at week 16 (188 diagnoses; 64.6% decrease compared with the same week in 2018-2019). Finally, there was a progressive increase of diagnoses during the last 2 weeks, but in the course of week 20, the number of diagnoses was 372, thereby being lower than those made during week 11.

❙Table 2❙ shows that the reductions in cancer diagnosis varied considerably as follows: minimal reduction in metastatic cancer (12.5%); moderate in non-Hodgkin lymphoma (24.3%), lung (27.4%), stomach (31%), liver (30.4%), and breast (38.2%) cancer; marked in bladder (43.6%), prostate (45%), colorectal (46.6%), and melanoma skin cancer (49.2%); and most marked in nonmelanoma skin cancer (69.9%). Overall, melanoma and nonmelanoma skin cancer represented 56.7% of all missing diagnoses of cancer in the lockdown period. On the contrary, the number of diagnoses of pancreas/biliary tract cancer disclosed a relevant increase in all but one institution (on average: +81.5%).

Among internal malignancies, insufficient resections of colorectal cancer were performed in the observation period
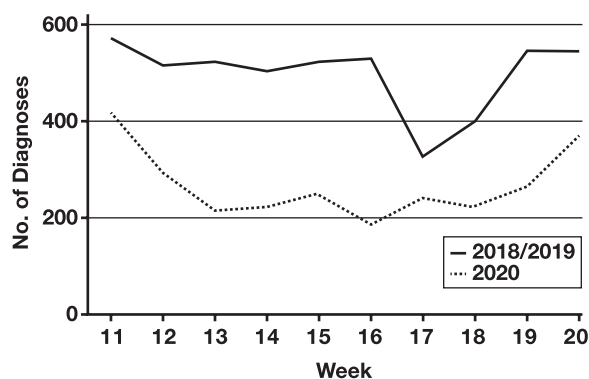

❙Figure 1❙ The week-to-week trend in the number of cellular pathologic diagnoses of cancer, with a fast decrease during the first 2 weeks, a nadir at week 16, and a progressive increase of the diagnoses during the last 2 weeks.

❙Table 2❙

Comparison Between the Number of New Diagnoses of Cancer Made in Weeks 11 to 20 of 2020 With the Number of Diagnoses Made in the Same Period of 2018 and 2019 (Given as an Average)

Diagnosis	2018-2019	2020	Δn (%)
Pancreas/biliary tract	27	49	+22 (81.5)
Metastasis	378.5	331	−56.5 (12.5)
Non-Hodgkin lymphoma	202	153	−49 (24.3)
Lung	175	127	−48 (27.4)
Liver	46	32	−14 (30.4)
Stomach	106.5	73	−33.5 (31.5)
Breast	620	383	−237 (38.2)
Bladder	351	198	−153 (43.6)
Prostate	429	236	−193 (45)
Colorectal	333.5	178	−155.5 (46.6)
Skin—melanoma	181	92	−89 (49.2)
Skin—nonmelanoma	1,688.5	508	−1,180.5 (69.9)

of 2020 to allow reliable assessment of prognostic data. Prostate plus bladder cancer accounted for 35.6% of the diagnostic decrease involving internal (noncutaneous) malignancies. For prostate, the number of diagnoses of high-grade lesions (prostatic cancer grading groups 4 and 5)[10] showed moderate variations (115 cases in 2018-2019 and 90 cases in 2020; 21.7% decrease); instead, the diagnostic decrease was most marked for low-grade lesions (314 cases in 2018-2019 and 146 cases in 2020; 53.5%). Regarding bladder cancer, the diagnostic decrease almost equally affected papillary and invasive neoplasms (45.2% and 41.1%, respectively).

Discussion

The pressure on health care systems due to the COVID-19 pandemic has hopefully passed the peak in Europe. Current projections, however, indicate that the COVID-19–related disruption may last for 18 months or more[11]; thus, health care prioritization and resource reallocation are warranted to minimize the negative impact of delayed diagnosis and therapy in oncology.

It has been estimated that even modest delays in surgery for cancer will incur a significant impact on survival, with a delay of 3 to 6 months expected to mitigate 19% to 43% of life years gained by hospitalization of an equivalent volume of admissions for community-acquired COVID-19.[11] These data, however, do not consider that further potentially avoidable cancer deaths may be due to the delay in clinical procedures aimed at achieving a cellular pathologic diagnosis. A previous internal standards–based audit showed that the COVID-19–related drop in colorectal cancer diagnosis was the most important area for action.[5] Such a study was based on a widely applicable audit model; however, its results were of little, if any,

general value because of the limited amount of data and because nonmelanoma skin cancer was not considered in the analysis.

In the present study, we compared the number of first diagnoses of malignancy during weeks 11 to 20 of 2020, 2019, and 2018 at seven pathologic anatomy units serving secondary care hospital networks in seven regions of northern and central Italy. Based on the ratio between the population served by the involved institutions (Table 1) and the total resident population, the collected data (Table 2) may represent one twelfth of all first cellular pathologic diagnoses of cancer made at all the secondary care hospital networks of the seven Italian regions.

The overall number of diagnoses steadily decreased during the first 2 weeks of the lockdown period and consistently increased during the last 2 weeks of the period, after a partial "reopening" of the economic and social life (Figure 1). At the end of the observation period, the trade-off for the COVID-19 pandemic in oncology was a 44.9% decrease (compared with 2018-2019) in cellular pathologic diagnoses of cancer, a decrease that most probably represented a diagnostic delay. An increase in the number of diagnoses was recorded only for carcinoma of the pancreas/biliary tract, probably as a result of its fast-rising incidence[12] coupled with its commonly impressive presenting symptoms.[13] To tackle the COVID-19–related backlog in the diagnosis of malignancy, we recommend for each institution internal auditing and reauditing, as per the previously suggested procedure,[5] to individuate the most critical areas for action, with the adoption of flexible strategies for staffing and for workflow organization.

Melanoma and nonmelanoma skin cancer represented 56.7% of all "missing diagnoses" in the lockdown period. A skin cancer triage system has been recently proposed on the basis of a multidisciplinary evaluation aimed at identifying four risk categories, only one of which requires immediate treatment because it has an oncologic risk greater than the COVID-19 risk ("green code"; ie, a patient with a clear-cut melanoma or a patient with advanced skin cancer under systemic treatment or radiotherapy).[14] The highest priority in suspected melanoma must be given to "palpable" (raised) tumors, because this clinical criterion is associated with a greater Breslow's thickness and/or with the nodular subtype.[15] Ex vivo dermoscopy with "dotting" of suspicious areas has been demonstrated to significantly reduce the need for recuts and the turnaround time for the diagnosis of melanocytic tumors[16] but cannot be implemented without specific training. For nonmelanoma skin cancer, scraping (Tzanck) cytology,[17] ideally with a rapid on-site evaluation by a cytopathologist, might be considered for preoperative evaluation because of its short turnaround time for diagnosis. Such a procedure is less reliable than biopsy but may be temporarily adopted because of time constraints.

Among internal malignancies, the 46.6% decrease in the number of diagnoses of colorectal cancer was especially concerning and confirmed on a larger scale the previously reported findings.[5] An observational cancer registry study from Taiwan on 39,000 newly diagnosed colorectal cancers found the risk of death significantly increased with diagnosis to treatment interval, across all cancer stages, as follows: for 31 to 150 days with a hazard ratio (HR) of 1.51 (95% confidence interval [CI], 1.43-1.59) and for 151 or more days with an HR of 1.64 (95% CI, 1.54-1.76) compared with an interval of 30 days or less.[18] The following corrective actions already have been proposed[5]: reintroduce mass screening by fecal occult blood test (and retain during any future lockdown conditions); promote the triage of patients by family physicians according to standard guidelines[19]; if wait times for colonoscopy are excessive, consider computed tomography colonography or double-contrast barium enema for patient triage; and on adequate biopsy samples, assess the tumor grade and undertake preoperative evaluation of the predictive markers (immunohistochemistry for mismatch repair proteins; mutation analysis for *KRAS*, *NRAS*, *BRAF*, and *PIK3CA*) based on their known prognostic value.[20]

Urologic cancers represented another critical area. For prostate, the clinical triage of patients was effective because high-grade tumors showed only a moderate decrease. In addition, since no adverse clinical outcome is expected even with a 12-month delayed surgery in high-risk prostatic cancers,[21] the COVID-19–related dysfunctions are expected to have a negligible clinical impact in this area. Regarding bladder cancer, the 41.1% diagnostic decrease almost equally affected papillary and invasive neoplasms (45.2% and 41.1%, respectively); thus, the clinical triage of patients needs to be improved. An early clinical identification of patients with putatively muscle-invasive bladder tumors is of paramount importance because delaying cystectomy by 90 days in pT2 or higher cases is associated with a higher pathologic stage and a worse prognosis.[22] A wider use of urinary cytology for clinical triage of patients may be helpful since most invasive bladder cancers show high-grade nuclear features and are thus readily identified on cytology specimens.[23] Some adjunct biomarkers on voided specimens (eg, UroVysion, uCyt, AccuDx-FDP, bladder tumor antigen test) may increase sensitivity in the diagnosis of invasive tumors.[23] An ongoing trial (ClinicalTrials.gov identifier:

NCT03962933) on mutation analysis of *FGFR3* and *TERT* promoters on urine specimens will probably help avoid cystoscopy in the follow-up of patients, thereby helping optimize resources and facilities.

In conclusion, the number of new or first metastatic diagnoses of malignancy at secondary care hospitals in northern and central Italy during the lockdown due to the COVID-19 pandemic (weeks 11-20 of 2020) was substantially lower than the same period of the previous 2 years (–44.9%). The drop in the diagnosis of cutaneous malignancies was the most relevant finding; among internal malignancies, colorectal cancer and invasive bladder cancer were the most critical areas. Forthcoming follow-up studies will hopefully evaluate the prognostic impact of the COVID-19–related delay in the diagnosis of melanoma and internal malignancies.

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