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COVID – 19 impact on Gastro-intestinal Cancer Treatment

A multicenter Italian retrospective study on COVID-19 pandemic condition and advanced Gastro - Intestinal Cancer

Are in Italy increased the new diagnosis of GI cancer in advanced stage in the 2020 compared with 2019, as a consequence of COVID-19?

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1. Background

The ongoing COVID-19 pandemic condition had a catastrophic consequence on the healthcare system. In order to contain the death from other diseases, such as cancer, the healthcare system still fights a challenging battle focusing the attention on COVD-19 without losing sight of other patient care. Routine screening and nonurgent surgeries reduced to increase capacity for COVID-19 patients complications. Moreover, it must take into account the fear for COVID-19 exposure of patients during the routine assessments.

Nevertheless, death related to other causes is not decreased. Standard cancer screening is decreased, such as colorectal cancer protocol which dropped by 84.5% through May 2020[1]. As a consequence, according to *London JW et al*, the incidence of new cancer diagnoses decreased of 65.2%[1]. As matter of fact, the new diagnosis of melanoma dropped by 67.1%, as well as the new diagnosis of lung cancer which dropped of 46.8%[1] in April 2020 compared to one year earlier.

Furthermore, the number of advanced gastrointestinal cancers are supposed to be increased in the surgical community. As conventional wisdom, the number of patients with locally advanced or metastatic gastrointestinal, as well as patients needing an emergency or a palliative procedure (i.e., stoma, feeding jejunostomy, gastroentero anastomosis) seems increased this year compared to 2019. These therapeutic delays may influence the long-term survival of these patients.

An increased rate of related death is expected, rising from 15.5% to 16.6% and 4.8% to 5.3 % for colorectal and lung cancer, respectively[2,3,4]. This study aims to investigate whether the main gastrointestinal cancers was diagnosed in a more advanced stage in 2020 compared to 2019 as a consequence of Covid-19 pandemic.

2. Methods

This is a multicenter retrospective study that will include patients treated for esophageal, gastric, pancreatic and colorectal cancer, from January 2019 to December 2020 in more than 50 Italian centers. All patients will be included in a disease-specific database, which will be sent to each Italian reference center. A minimum of 1.000 patient/year is expected to show a significative difference between the considered years.

The primary endpoint is to show if in Italy the number of cancer mentioned above, was diagnosed in a more advanced stage (i.e. > I stage, Metastatic disease) in 2020 compared to 2019 as a consequence of COVID-19 pandemic condition.

Secondary endpoints are:

1. To show any difference in the rate of cancer related neo-adjuvant therapy in 2020 compared to 2019;
2. To show any difference in the rate of cancer related palliative procedures/ bridge therapy in 2020 compared to 2019, before starting with standard treatment;
3. To show any difference of patients unable to performer cancer related preoperative chemo or radiotherapy in 2020 compared to 2019 due to scarce performance status or for symptomatic disease;
4. Rate of patients unable to performer cancer related adjuvant therapy in 2020 compared to 2019 due to scarce performance status

Inclusion criteria

- Patients submitted to elective surgery for esophageal, gastric, pancreatic and colorectal cancer in the year 2019-2020;
- Patients submitted to emergency surgery/procedure (Interventional radiology, endoscopic procedure) for complication (i.e. perforation, bleeding, occlusion) secondary to esophageal, gastric, pancreatic and colorectal cancer in the year 2019-2020;
- Patients submitted to palliative surgery/procedure (i.e. stoma, GEA, external biliary drainage, feeding jejunostomy) for esophageal, gastric, pancreatic and colorectal cancer in the year 2019-2020;
- Patients undergoing preoperative chemo or radiation therapy for locally advanced or metastatic esophageal, gastric, pancreatic and colorectal cancer in the year 2019-2020;
- Patients undergoing to adjuvant therapy after esophageal, gastric, pancreatic and colorectal cancer I surgery in the year 2019-2020

Exclusion Criteria

- Patients under 18 years old and over 85 years old;
- Patients with multiple tumors.

Outcome measures

For any cancer will be requested:

- Preoperative Outcomes: age, gender, BMI, Charlson Comorbidity Index, ASA, nutritional status, diagnostic tool, date of diagnosis, ECOG performance status, Symptoms, Localization, Histopathological diagnosis, Clinical Staging, eventual bridge to surgery or preoperative chemotherapy, the start date of eventual preoperative chemo or radiation therapy was started, inability for preoperative treatment, Bilirubin and Hb value, Prognostic nutritional index.

- Perioperative Outcomes: date of surgery, COVID Test, type of procedure, type of approach, associated procedures, hospital stay, 30 days postoperative complications, 30 days mortality, 30 days readmission.
- Postoperative Outcomes: pTNM stage, grading, tumor's diameter, number of total lymph nodes, number of positive lymph-nodes, resection margin, neural invasion, lymphovascular invasion, molecular characteristic of cancer, date when eventual adjuvant therapy was started, inability to complete adjuvant therapy.

All the data will be collected in the aforementioned databases. The preoperative data will contain the demographic data, the Charlson Comorbidity Index (calculated with www.mdcalc.com/charlson-comorbidity-index-cci), the way to obtain the diagnosis (routine screening or clinical assessments or in the emergency department), data of diagnosis (data of endoscopy or CT scan or the data of histopathological diagnosis), ECOG performance status, localization of the tumor according to the specific type of cancer (i.e. superior, middle or inferior for esophageal cancer; Siewert classification for adenocarcinoma of the cardias), Histopathological diagnosis (i.e. adenocarcinoma, GIST, NET, squamous cancer), clinical staging. Furthermore, will be requested any procedure used as a bridge to chemo/radiation therapy or surgery, start date of preoperative treatment (neoadjuvant therapy for locally advanced cancer or chemotherapy for metastatic disease), preoperative chemo and radiation therapy protocol, the number of cycles performed/total, early discontinuation of preoperative treatment and its cause (pharmacological toxicity or other causes), ycTNM, bilirubin and Hb value, Prognostic nutritional index.

The perioperative data will include the date of surgery, COVID-19 test response (only from January 2020), Intraoperative findings (i.e. metastatic disease, carcinomatosis), the purpose of surgical procedure (curative or palliative), the extension of resection (cancer-related - i.e. partial or total gastrectomy), surgical approach (minimally invasive or open procedure), conversion to open, associated surgical operations (related or not with the disease – i.e. liver wedge resection for metastatic disease, cholecystectomy, feeding jejunostomy), hospital stay, 30 days complications (according to Clavien-Dindo classification), type of complications (medical or surgical complications), 30 days readmission and mortality.

Postoperative outcomes will include pathological TNM, grading, cancer diameter, number of retrieved lymph nodes, number and location of positive lymph nodes, resection margin status, lymphovascular invasion, neuronal invasion, molecular characteristic of cancer (i.e. HER status, MSI status). Furthermore, it will be considered the number of the chemotherapy cycle performed and the starting date. Early discontinuation of adjuvant therapy and its cause (hematological/cardiological other toxicity).

The data recruitment period runs from- January 2021 to - March 2021.

Sample size

The expectation is to include at least 1000 patients/year for this study into the sample size, likely divided evenly over the two years of study (2019 and 2020) and between the different centers included in the study. This number would allow to obtain a power of the proposed statistical tests equal to 99% and a level of significance in the range between 5% and 1%. MICE (Multivariate Imputation via Chained Equations) will be the procedure used to impute missing data for explanatory variables; with this approach, instead of imputing all missing values with a single value (mean/ median), the statistical information deriving from the distribution of the other variables is taken into account, conceiving the missing values as an outcome to be predicted. This allows to take into consideration the correct variability in the whole dataset, and to obtain estimates that are as unbiased as possible.

Statistical Analysis

The quantitative variables included in the study will be presented through the mean ± the standard deviation, the median and the range (distance between maximum and minimum values), both at general level and divided by year and by center. The qualitative (categorical) variables will be represented as percentages and absolute values, both at a general level and divided by year and center. It will be evaluated, if necessary, to carry out a case matching procedure between the two years under analysis (2019 and 2020), by means of the "nearest neighbor matching" technique, if confounding variables may be significantly different in the two groups. The comparison between quantitative variables of interest., will be performed through the two-tailed Student T-Test (in case of heteroskedasticity of variances) or with non-parametric tests, such as the Mann-Whitney U test or the Kruskal-Wallis test. The comparison between qualitative variables of interest (number of patients, number of patients with stage III and IV, number of metastatic patients, number of patients who have undergone chemo and radio therapy pre and post-operative, emergency interventions caused by the tumor) will be carried out to evaluate the association or not among them, through an extension of the Chi-Square Test, suitable for multi-centric studies (the Cochran – Mantel – Haenszel Test). The respective Odds Ratios, linked to the potential associations among variables, will be computed alongside overall significance.

Ethics and dissemination

The study will be conducted in accordance with the Declaration of Helsinki and respecting the guidelines on good clinical practice, principles E6 (R2). The study requires approval by the ethics committee of the coordinating center (Comitato Etico di Area Vasta Sud Est Dipartimento Politiche del Farmaco e Attività Farmaceutiche Segreteria Amministrativa) then registered at ClinicalTrial.gov.

Thereafter, all the participating centers will obtain authorization to participate from the local institutional review board.

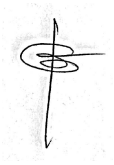
To all participating investigators will be confirmed the authorship for written publications (2 investigator for each center). Anonymized participant-level datasets will be available after study completion upon reasonable request by contacting the principal investigator.

The results of the study will be presented at international or national congress and published in surgical or oncological journals.

Giuseppe Giuliani, MD

COVID - AGICT study group coordinator

Chief investigator.



References

1. London JW, Fazio-Eynullayeva E, Palchuk MB, et al: Effects of the COVID-19 pandemic on cancer-related patient encounters. JCO Clinical Cancer Inform. 2020;4: 657-665. doi: 10.1200/CCI.20.0006
2. Epic Health Research Network. Preventive cancer screenings during COVID-19 pandemic. May 1, 2020. Accessed August 20, 2020. https://www.ehrn.org/wp-content/ uploads/Preventive-Cancer-Screeningsduring- COVID-19-Pandemic.pdf
3. Maringe C, Spicer J, Morris M, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol. 2020;21(8):1023-1034. doi:10.1016/S1470-2045(20)30388-0
4. Sud A, Jones ME, Broggio J, Loveday C, Torr B, Garrett A, Nicol DL, Jhanji S, Boyce SA, Gronthoud F, Ward P, Handy JM, Yousaf N, Larkin J, Suh YE, Scott S, Pharoah PDP, Swanton C, Abbosh C, Williams M, Lyratzopoulos G, Houlston R, Turnbull C. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. Ann Oncol. 2020 Aug;31(8):1065-1074. doi: 10.1016/j.annonc.2020.05.009. Epub 2020 May 19. PMID: 32442581; PMCID: PMC7237184.