

Management of Cancer Patients During the SARS-CoV-2 Pandemic, in a County in Romania

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Abstract: Introduction. The SARS-CoV-2 pandemic has profoundly affected health systems by relocating resources, enforcing restrictive measures and burdening health care workers. The study aims to assess the changes in the treatment and the evolution of cancer patients in a county in Romania, with a population of over a half million inhabitants. Patients and method. Patients with breast, gastric, colorectal, and lung cancer were studied over a two-year period: 14 months before the onset of the pandemic and 10 months after its beginning. The number of new cases of cancer, the number of chemotherapy and radiotherapy sessions, the number of surgeries and deaths from these four types of cancer were recorded. Results. During the pandemic, fewer chemotherapy sessions were administered for all cancers ($p < 0.0001$). The number of radiotherapy sessions for breast ($p < 0.007$) and colorectal cancer ($p < 0.002$) increased by banning patients from going to university hospitals and decreased for lung cancer ($p < 0.03$) which has symptoms similar to those of the SARS-CoV-2 virus. Conclusions. Cancer patients had limited access to chemotherapy. Their diagnosis and treatment were included in the same category as non-life-threatening diseases. Testing, quarantine and travel limitation were not accompanied by additional safe medical services for the oncological patients. The death rate is inconclusive because the time since the onset of the pandemic is shorter than the natural evolution of the types of cancers studied.

Keywords: Cancer, Pandemic, COVID-19, Chemotherapy, Radiotherapy, Surgery, Mortality, Discrimination, Lockdown, Triage, Policy

1. Introduction

The outbreak of the pandemic with Covid-19 caused a profound disruption in the Romanian health system, one of the least performing in Europe, with a poor equilibrium, affected by events to which the authorities, health professionals, the media and the population have often reacted inappropriately: the crisis of the great burns from Colectiv [1], the fires in the Giulești Maternity Hospital [2] or in the intensive care units [3].

The first case of Covid-19 infection was confirmed in Romania on February 26, 2020, and in Maramureș County on February 28, 2020, county with a population of 519,386 inhabitants on the 1st of July 2020. The first preventive

measures were taken on January 22 and the state of emergency and lockdown measures were imposed on March 16 of the same year.

An important category of patients affected by pandemic restrictions are cancer patients who require chronic long-term treatment and have immunity affected by neoplasia and its associated treatments, being among the most likely to contact a severe infection with the new coronavirus [4]. In Maramureș County, cancer patients have several treatment alternatives:

- Baia Mare County Emergency Hospital, tertiary hospital, with oncology, radiotherapy and surgery departments, the

main provider of health services for oncology patients in the county, with 990 beds,

a municipal hospital and a city hospital, with surgery wards and only the municipal hospital with oncology department,

two private medical centers with oncology departments,

in Cluj County, the university hospitals in Cluj Napoca, at a distance of 150 km, with oncology, radiotherapy and surgery services.

At the beginning of the pandemic, the authorities had contradictory reactions: The National Health Insurance House has given the possibility to the attending physicians to decide themselves whether to initiate, continue or stop the treatments for oncological patients, through an issues statement on March 23rd, 2020, but the next day, on March 24th, the Order of the Minister of the Interior suspended all hospitalizations and non-emergency operations for a period of 14 days, although less than 800 cases were confirmed throughout the country. The media has contributed to the chaos with alarming news and repeated images with a strong emotional impact (e.g. ambulance carrying patients suspected of having coronavirus infection with a special isolation unit like a shuttle).

On the other hand, hospitalized cancer patients have an increased risk of developing nosocomial infection with COVID-19 [5], but the ESMO's recommendation is to test cancer patients and place them in facilities with 0 SARS-CoV-2 infection, so as not to interrupt treatment, depending on the economic resources and the pressure of the pandemic for each hospital [6].

Our study aims to compare the treatment of cancer patients before the pandemic, with their management after its onset and the impact that the state of emergency and alert had on the evolution of these patients in Maramureș County in Romania.

2. Methods

We conducted a retrospective study on the population of Maramureș County, located in northern Romania, which had on July 1st 2020 a number of 519,386 inhabitants. The study included patients with 4 types of cancer: breast, gastric, colorectal and lung. For gastric cancer, patients with esogastric junction cancer were also included in the study, colon

and rectal cancers were considered together, and lung cancers covered all cancers with this localization. The following data were registered in the period 1.01.2019 - 31.12.2020:

the number of new cases and deaths registered in the National Cancer Registry,

the number of chemotherapy and radiotherapy sessions, as well as the number of operations performed for each type of cancer, from the databases of the hospitals that performed these medical services: Baia Mare County Emergency Hospital, Sighetu Marmăției Municipal Hospital, Vișeu de Sus City Hospital and the two private medical centers. We did not consider immunotherapy sessions.

3. Data Analysis

The data recorded monthly from two periods were compared: 1.01.2019 - 28.02.2020 (14 months) - pre-pandemic period and 1.03.2020 - 31.12.2020 (10 months) - pandemic period with COVID-19. Statistical analysis was performed with the following types of tests:

Unpaired t-test, when the distribution and variation (standard deviation) were normal in the two groups,

Unpaired t-test with Welch's correction, when the distribution was normal but not the variation,

Mann-Whitney test, when the distribution was not normal.

Statistical significance was considered for $p < 0.05$. Statistical analysis was performed using Graph Pad Prism 9 (Graph Pad Software Inc., La Jolla, CA, USA).

4. Results

The most common cancers registered between 1.01.2019 and 31.12.2020 were colorectal (361 patients), followed by lung (310 patients), breast (243 patients) and gastric (174 patients). Comparing the two time periods (prepandemic and pandemic) we found that in the pandemic months, there were fewer newly detected lung cancers (average 11.1 vs. 14.21), colorectal cancer (average 14.8 vs. 15.21) and gastric (mean 6.2 vs. 7.92) and more breast cancers (mean 10.8 vs. 9.64) compared to the months before the pandemic (Table 1). None of these comparisons had statistical significance, although the decrease in new cases of lung cancer approached this ($p=0.0521$).

Table 1. New cases of cancer recorded over 24 months expressed as mean±standard deviation.

Type of cancer	The months before the pandemic (n=14)	Months after the pandemic began (n=10)	p
Breast	9.64 (±1.98)	10.8 (±3.96)	0.41
Gastric	7.92 (±3.52)	6.2 (±2.57)	0.2
Colorectal	15.21 (±4.85)	14.8 (±4.1)	0.82
Lung	14.21 (±4.02)	11.1 (±3.07)	0.05

During the pandemic, the number of chemotherapy sessions decreased statistically significantly, with $p < 0.0001$, in all four cancers studied (Table 2).

The number of surgeries increased for gastric (mean 1.6 vs.

1), colorectal (mean 11.9 vs. 9.64) and lung (mean 0.2 vs. 0.14) cancers, and those for breast cancer decreased (3.4 vs. 4.78) in Maramureș County during the pandemic (Table 3), but without being statistically significant.

Table 2. Number of chemotherapy sessions recorded between 1.02.2019 - 31.12.2020, expressed as mean±standard deviation.

Type of cancer	The months before the pandemic (n=14)	Months after the pandemic began (n=10)	p
Breast	147.9 (±13.32)	102.5 (±17.28)	<0.0001
Gastric	52.07 (±6.08)	30.9 (±10.09)	<0.0001
Colorectal	154.5 (±22.02)	108.2 (±15.87)	<0.0001
Lung	120.5 (±8.48)	92.8 (±13.3)	<0.0001

Table 3. Number of operations performed before and during the pandemic, expressed as mean±standard deviation.

Type of cancer	The months before the pandemic (n=14)	Months after the pandemic began (n=10)	p
Breast	4.78 (±2.54)	3.4 (±1.83)	0.15
Gastric	1 (±1.03)	1.6 (±1.57)	0.38
Colorectal	9.64 (±3.87)	11.9 (±3.92)	0.13
Lung	0.14 (±0.36)	0.2 (±0.42)	>0.99

The only radiotherapy laboratory in Maramureş County, equipped with a linear accelerator with 2 photon energies of 6, respectively 15 MV and a CT simulator for simulating treatment plans, has been operating since May 2019. The number of radiotherapy sessions (Table 4) increased

statistically significantly during the pandemic for breast (mean 147.2 vs. 69.07) and colorectal (mean 73.8 vs. 32.93) cancers and decreased for gastric cancers (mean 7.9 vs. 9.64) and pulmonary cancers (mean 15 vs. 28.5). For the latter, the decrease was statistically significant ($p=0.03$).

Table 4. Number of radiotherapy sessions performed between 1.02.2019 - 31.12.2020, expressed as mean±standard deviation.

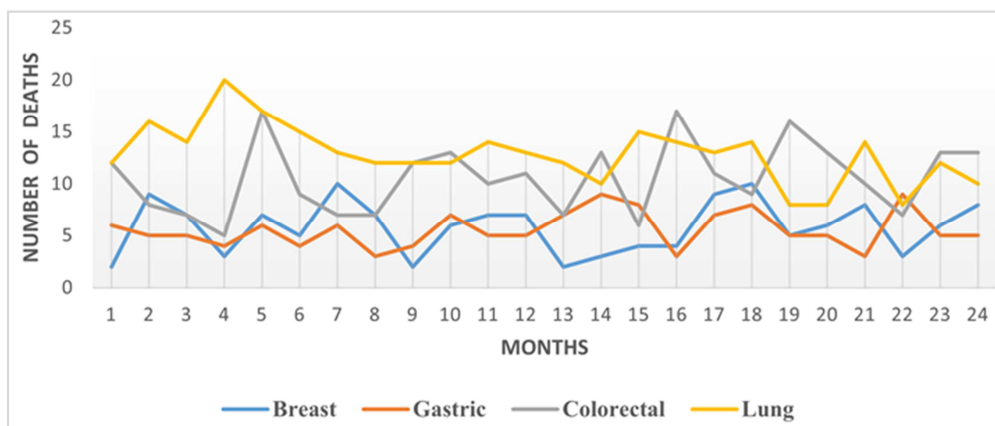
Type of cancer	The months before the pandemic (n=14)	Months after the pandemic began (n=10)	p
Breast	69.07 (±51.04)	147.2 (±57.84)	0.007
Gastric	9.64 (±13.07)	7.9 (±7.76)	0.93
Colorectal	32.93 (±32.93)	73.8 (±73.8)	0.002
Lung	28.5 (±19.77)	15 (±8.43)	0.03

Deaths from breast, gastric, colorectal, and lung cancers are shown in Figure 1. None of the four cancers changed statistically significantly after the onset of the pandemic.

After the onset of the pandemic, there were more deaths from breast, stomach, colon and rectal cancer, but fewer from lung, as shown in Table 5.

Table 5. Breast, gastric, colorectal and lung cancer deaths before and during the pandemic, expressed as mean±standard deviation.

Type of cancer	The months before the pandemic (n=14)	Months after the pandemic began (n=10)	p
Breast	5.5 (±2.68)	6.3 (±2.35)	0.45
Gastric	5.42 (±1.55)	5.8 (±2.09)	0.62
Colorectal	9.85 (±3.3)	11.5 (±3.59)	0.25
Lung	13.71 (±2.58)	11.6 (±2.83)	0.21

**Figure 1.** Deaths from cancer 1.01.2019-31.12.2020.

5. Discussion

The COVID-19 pandemic has put pressure on all specialties that offer curative treatment to cancer patients in order to reduce consultations, hospitalizations and treatments:

surgeons, oncologists and radiologists. The hospitals in Maramureş County are the lifeline for the patients who were treated during the pandemic in the university clinics in Cluj-Napoca, who did not receive them anymore for treatment. However, these specialties approached cancer patients differently. Admissions to oncology wards were made only

after testing, if patients were negative, otherwise they had to wait 14 days for the quarantine to end in order to receive treatment in a clean oncology ward without COVID-19. On the other hand, compliance with the spacing rules reduced the number of hospitalized patients by one third each month, in order to reduce the risk of infection in immunocompromised cancer patients [7]. The statistically significant decrease in the number of chemotherapy sessions for breast, gastric, colon, rectal and lung cancers ($p < 0.0001$ in all cases) was also due to the deployment of specialists from these departments to triage points and absences due to SARS-CoV-2 health workers' infections.

The surgeons' strategy was different. With the support of the authorities, a general surgery department was set up for the patients tested positive [8], and the rest of the surgery departments in the county remained operating for asymptomatic patients, who were not tested, but who underwent epidemiological triage. The number of breast cancer surgeries, which is closely linked to neoadjuvant cancer treatment, has also decreased during the pandemic. However, the number of operations for gastric, colorectal and lung cancer has increased, having as main cause the reduction of the possibility of patients moving to university centers during the pandemic. The decision to operate was an eclectic one, based on the decision of each surgeon, which varied from the operation of cancers only with complications, to the operation of all cancers, so as not to have a second pandemic of cancer deaths, due to delayed treatment [9]. The pandemic forced the deployment of surgery staff to cover the ward for positive patients and affected staff who were quarantined for 14 days when they became infected, but without hospitalizations and deaths. On the other hand, it was the decision of the patients to be hospitalized and to be operated, many of them postponing the presentation to the surgeon due to the fear of contamination in the hospital with new coronavirus.

The radiotherapy department of the Baia Mare Emergency Hospital received all the patients who needed this treatment, including those who could not go to university centers. The number of breast ($p < 0.007$) and colorectal ($p < 0.002$) cancer patients who were irradiated neoadjuvant or palliative during the pandemic increased statistically significantly. Palliative radiotherapy for gastric cancers decreased statistically insignificantly ($p = 0.93$), as rapidly evolving head and neck tumors, hemorrhagic or compressive tumors were prioritized for radiotherapy [10]. Patients with gastric cancer were irradiated only to alleviate local symptoms: bleeding, pain, or obstruction [11]. Lung tumors received less radiological treatment during the pandemic months ($p = 0.03$) due to the particularities [12] of this group of patients:

the worsening symptoms of lung cancer are similar to those of SARS-CoV-2 infection,

the radiological images of the lungs of these patients with pneumonia due to radiotherapy, chemotherapy or immunotherapy are similar to those suggestive of COVID-19 infection [13].

On the other hand, with respiratory symptoms, lung cancer patients avoided coming into contact with the hospital during

the pandemic months.

Diagnosis of cancers during the COVID-19 pandemic decreased the number of newly registered cases due to restrictions imposed in family doctors' offices, outpatient clinics and hospitals [14, 15]. In our study, this decrease was recorded for gastric ($p = 0.20$), colorectal ($p = 0.82$) and lung ($p = 0.052$) cancers, but without reaching statistical significance, although it was close to it in lung cancers, probably due to diagnostic difficulties in patients with respiratory symptoms [12]. However, the number of newly registered breast cancers increased, without reaching statistical significance ($p = 0.41$), although in Romania there are no screening programs for breast cancer. CT studies for the diagnosis of SARS-CoV-2 pneumonia incidentally found macro calcifications and tumor masses in the breasts [16], which therefore increased the number of newly registered cases.

Although statistically insignificant, mortality increased in pandemic months for breast ($p = 0.45$), gastric ($p = 0.62$) and colorectal ($p = 0.25$) cancers probably due to delayed diagnosis and specific treatment, with the rules imposed by the pandemic [17, 18]. It is likely that this increase will reach statistical significance in the coming months, when the natural history of these cancers will bring them to an end, and the delay in treatment will have the expected negative effect.

The number of chemotherapy sessions was lower in the pandemic months mostly due to the fact that only patients which tested negative or the ones that had negative tests after being positive underwent treatment. The same restrictions could also be the reason why the number of deaths increased for breast, gastric and colorectal cancers during the pandemic. However, the authorities and hospitals in Maramureş County did not create oncology wards for COVID-19 positive patients, as they set up a surgery ward for them. Admission of patients tested positive in the oncology department was prohibited to limit the nosocomial spread of the virus and contamination of health workers [19, 20].

On the other hand, only the spread of the virus through saliva droplets has been documented, its persistence in air being uncertain [21, 22]. This means that the isolation of asymptomatic positive COVID-19 patients in each hospital ward, in compliance with hygiene measures (wearing masks, personal protective equipment - PPE, hand hygiene, etc.), would have possibly been sufficient to prevent nosocomial infections and would have allowed the administration of oncological treatments in a non-discriminatory manner.

6. Conclusion

The evolution of patients with breast, gastric, colorectal and lung cancer in Maramureş County has been modified by the appearance of the pandemic and the imposition of related safety measures, but the long-term results of the treatment of these patients will probably be in the future even more affected than in the first 10 months of pandemic studied.

The pandemic affected both patients and staff. The oncologic patients were not only discriminated, with priority being granted to SARS-CoV-2-infected patients, but they also had to suffer due to the lack of infrastructure necessary

for the safe diagnosis and treatment of cancer.

Testing, quarantine, and travel reduction have not been offset by the medical facilities to support cancer patients, especially since cancer was considered one of the common diseases that do not endanger patients' lives by delaying diagnosis or treatment.

Cancer patients in Maramureş County turned to the nearest specialized services available, but they did not receive proper treatment due to the low addressability during the pandemic.

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