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Impact of COVID-19 Pandemic on Non-Melanoma Skin Cancer's Tumor Burden and Care: a Multi-Center Study Based in Northern Italy

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Summary The brisk remodeling in healthcare delivery observed after the COVID-19 outbreak led us to evaluate how the pandemic affected non-melanoma skin cancer's (NMSC) care and tumor burden. To address this topic, we set up a retrospective real-life multi-center study based on the cities of Bergamo and Varese, whose provinces were the worst hit in Italy by the pandemic. We analyzed medical and pathological data from patients that underwent surgery in the two months preceding the outbreak in Italy and compared them to those who did in the corresponding bimester of the following year, reaching 214 patients and 274 lesions. We observed a considerable and significant increase in NMSC's diameter, as well as in the proportion of squamous cell carcinomas. Both the average waiting time to obtain an evaluation visit and the average time in the surgical waiting list was shorter after the COVID-19 outbreak: the reason is that we evaluated and operated near-exclusive patients affected by high-priority lesions, who benefited from "fast-track" referrals. Conversely, less-concerning lesions were, and still are, left on hold, until they will become advanced enough to be labeled as "urgent". Plastic surgery departments should evade as soon as possible from this downward spiral, in order to provide our patients with timely cancer care and to be able to treat all plastic surgery-requiring pathologies.

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Introduction

On January 30, 2020, the World Health Organization labeled the novel SARS-CoV-2 coronavirus a public health emergency.¹ Italy was the first European nation to be severely affected by COVID-19, and the related crisis is estimated to be the most serious historical event in terms of human and economic loss, after World War II.² The first wave of the pandemic mainly affected the northern part of the Country, with Lombardy being the most severely affected region.³ The province of Bergamo was considered to be the epicenter of the Italian outbreak and experienced a 4.07-fold increase in terms of overall deaths, as compared to the same segment of 2019.⁴ After a progressive and significant descent, in late August 2020 began the so-called second wave, reaching a second peak on November 13, 2020.⁵ This time the whole country was involved, even though Lombardy was once again the most affected region.⁶ The Bergamo area was relatively less affected, whereas Varese was the worst-hit province, with over 5,000 cases per 100,000 citizens recorded throughout the time span between July 17, 2020 and December 28, 2020.⁷

In this scenario, according to both local and national directives, the whole healthcare providing system reorganized itself in order to deal with the shortage of hospital personnel, ICU beds, and ventilators and to maximize social distancing.⁸ As a result, all surgical activities were put on hold, except for emergency surgery, urgent transplantation, and appropriate cancer treatment.⁹

This brisk remodeling in healthcare and cancer-care delivery led us to evaluate its impact on non-melanoma skin cancer's (NMSC) local behavior. To address this topic, we set up a retrospective real-life multi-center study in which the authors combined medical records and pathological data from Papa Giovanni XXIII Hospital in Bergamo and Ospedale di Circolo in Varese.

Materials & methods

To build up this series, we searched histological reports from the Pathology Departments of Papa Giovanni XXIII Hospital in Bergamo and Ospedale di Circolo in Varese. We considered all consecutive histological reports regarding skin cancer removal by the Plastic Surgery Department. The two timeframes under examination were the one from December 1, 2019 to January 31, 2020 and the one from December 1, 2020 to January 31, 2021. Then, we selected all the records that reported a basal cell carcinoma (BCC) or cutaneous squamous cell carcinoma (cSCC) diagnosis.

For each malignant lesion, we registered (i) patient general information (age and gender), (ii) day of surgery, (iii) histological diagnosis, (iv) greater tumor dimension in millimeters, (v) anatomical site of excision, and (vi) status of the margins (i.e., complete or incomplete excision).

We cross-checked these data with our electronic medical records and examined: (i) booking date of first plastic surgery visit and (ii) recruitment date in the plastic surgery waiting list.

Subsequently, for every patient, we calculated how many days passed: (i) between booking and visit and (ii) between recruitment and surgery.

Data were analyzed using Student's *t* test for continuous variables, and Fisher's exact probability test for dichotomous variables. P-values were considered statistically significant if inferior to 0.05 and extremely statistically significant if inferior to 0.001.

Results

We evaluated a total of 274 lesions and 214 patients. Patients' and lesions' characteristics are summarized in [Table 1](#) and [Table 2](#), respectively.

From December 1, 2019 to January 31, 2020, we operated 121 patients, of which 44 (36.4%) were women and 77 (63.6%) were men. The mean age at time of surgery was 75.5 years (95% CI 73.5-77.5, median = 78). Since patients booked a medical appointment in the Plastic Surgery Department, they waited on average 34.7 days (95% CI 19.4-50.1) to be evaluated and put on surgical list. From that moment, additional 97.9 days (95% CI 84.7-111) went by before they received surgical treatment. Since 28 patients had multiple excisions, 164 NMSC were surgically removed and analyzed, of which 45 were cSCC (27.4%) and 119 were BCC (72.6%). The lesions' diameter was on average 13.3 mm (95% CI 11.6-15, median = 10 mm) for all lesions, 19.5 mm (95% CI 15-24, median = 17 mm) for cSCCs, and 10.9 mm (95% CI 9.6-12.2, median = 10 mm) for BCCs. Complete excision was not achieved in 19 (11.6%) cases, entailing subsequent radicalization surgery. Cancers were located in 129 cases (78.7%) in the head and neck area and in 110 cases (67.1%) in the face.

From December 1, 2020 to January 31, 2021, 93 patients underwent surgery, of which 31 (33.3%) were women and 62 (66.7%) were men. On average, they were 76.5 years old (95% CI 74.2-78.8, median = 80). These patients waited for a mean time of 28.4 days (95% CI 18.2-38.6) to have an evaluation appointment and, from that moment, 80.3 days (95% CI 63.9-96.7) to have their lesion(s) surgically removed. In 10 patients more than one tumor was removed, therefore, 110 NMSC were analyzed: 49 (44.5%) cSCCs and 61 (55.5%) BCCs. From pathological data, the mean diameter was 22.7 mm (95% CI 19.2-26.2, median = 16.5 mm) for all lesions, 29.8 mm (95% CI 23.9-35.6, median = 25 mm) for cSCCs, and 17 mm (95% CI 13.3-20.7, median = 13 mm) for BCCs. The excision was incomplete in 11 (10%) cases. The anatomical site of excision was the head and neck area in 94 (85.5%) cases and the face in 77 (70%) cases.

While comparing demographic features of the patients we operated, we found statistical difference neither in gender proportions ($p = 0.117$) nor in the mean age at diagnosis (-0.94 years, $p = 0.542$).

Both the mean time between booking and evaluation visit with the plastic surgeon and the mean time in the surgical waiting list was shorter in December 2020-January 2021 (-6.3 days and -17.6 days). However, these differences were not significant ($p = 0.492$, $p = 0.093$, respectively).

The mean dimension of all lesions excised in December 2020 and January 2021 showed a substantial increase ($+9.4$ mm, 95% CI 5.5-13.2); this difference proved to be extremely statistically significant ($p < 0.0001$). This variation was confirmed when we stratified data per histological type: cSCCs presented a mean increase of 10.3 mm (95% CI 3-17.6)

Table 1 Demographic and medical features of patients included in this study.

| | December 2019-January 2020 | December 2020-January 2021 | Δ | p |
|---|-------------------------------|-------------------------------|-------|-------|
| Sex | | | | |
| Male | 77 (63.6%) | 62 (66.7%) | -15 | 0.679 |
| Female | 44 (36.4%) | 31 (33.3%) | -13 | 0.352 |
| Age at diagnosis (yrs) | 75.5 (73.5-77.5) | 76.5 (74.2-78.8) | -0.94 | 0.542 |
| Time from booking to evaluation (days) | 34.7 (19.4-50.1) | 28.4 (18.2-38.6) | -6.3 | 0.492 |
| Time in surgical waiting list (days) | 97.9 (84.7-111) | 80.3 (63.9-96.7) | -17.6 | 0.093 |

Table 2 Characteristics of excised lesions.

| | December 2019-January 2020 | December 2020-January 2021 | Δ | p |
|----------------------------|-------------------------------|-------------------------------|-------|---------|
| Diagnosis | | | | |
| cSCC | 45 (27.4%) | 49 (44.5%) | +4 | <0.05 |
| BCC | 119 (72.6%) | 61 (55.5%) | -58 | <0.05 |
| Mean diameter - total (mm) | 13.3 (11.6-15) | 22.7 (19.2-26.2) | +9.4 | <0.0001 |
| Mean diameter - cSCC (mm) | 19.5 (15-24) | 29.8 (23.9-35.6) | +10.3 | <0.05 |
| Mean diameter - BCC (mm) | 10.9 (9.6-12.2) | 17 (13.3-20.7) | +6.1 | <0.05 |
| Incomplete excisions | 19 (11.6%) | 11 (10%) | -8 | 0.68 |
| Site | | | | |
| H&N | 129 (78.7%) | 94 (85.5%) | -35 | 0.156 |
| Face | 110 (67.1%) | 77 (70%) | -33 | 0.557 |

and BCCs of 6.1 mm (95% CI 2.2-10). Both differences were statistically significant ($p = 0.0062$ and $p = 0.0025$, respectively).

In December 2020-January 2021, we observed an absolute and percent increase in cutaneous SCC diagnoses, if compared to the previous year (44.5% versus 27.4% of the total). This difference was also statistically significant ($p = 0.004$).

On the contrary, no significant ($p = 0.699$) was the difference observed in the rate of incomplete excisions: 19 cases (11.9%) in December 2019-January 2020 versus 11 cases (10%) in December 2020-January 2021.

In both series, most lesions were located in the head and neck district, especially on the face. Minor differences in proportions were observed (78.7% versus 85.5% for the head and neck, 67.1% versus 70% for the face), without any statistical significance ($p = 0.205$ and $p = 0.692$, respectively).

Discussion

In December 2019, the world awoke to a new zoonotic strain of coronavirus that was named SARS-CoV2. After the COVID-19 outbreak, the primary risk for patients with cancer is the inability to receive necessary medical services in a timely fashion, especially in high-risk epidemic areas, where there is a high demand of medical staff and facilities.¹⁰ Because of cancer's worsening nature, postponing treatment or screening may allow the disease to reach more advanced stages.¹¹ This phenomenon has already been confirmed for cutaneous melanoma by Ricci et al.; they observed an increase in mean Breslow thickness post-lockdown (1.96 mm), if compared

to pre-lockdown lesions (0.88 mm), supporting the hypothesis that during the COVID-19 lockdown, the diagnoses of melanoma may have been delayed.¹²

NMSCs are the most common human malignancies, being 18-20 times more frequent than cutaneous melanoma, and their incidence is steadily rising worldwide.¹³ BCC and squamous cell carcinoma (SCC) account for about 99% of all NMSCs.¹⁴

Due to the slow natural history of this malignancy, BCCs are at a low risk of significant progression and mortality as a result of a treatment delay, and the National Comprehensive Cancer Network (NCCN) recommends deferring treatment during the COVID-19 pandemic for at least 3 months unless the patient is highly symptomatic.¹⁵

SCCs cause as many deaths in the USA as melanoma.¹⁶ The overall risk of metastasis is 3.7-5.2%, with 2.8% disease-specific mortality¹⁷; both are higher in case of large tumor dimensions (≥ 2 cm).¹⁸ Treatment delay for patients with cSCC is associated with some interval enlargement of the tumor. Consistently, the NCCN states that treatment can be deferred, but clinicians should consider excision if the tumor poses a risk of metastasis or debilitating disease progression within 3 months.¹⁵

We arranged this multi-center retrospective observational study in order to evaluate how the COVID-19 pandemic affected NMSC care. To this end, we evaluated skin lesions that were excised between December 1, 2020 and January 31, 2021 (i.e., after the second wave of the pandemic) and compared them to those of the two months preceding the pandemic outbreak in Italy (i.e., December 2019 and January 2020). Our series comes from the aggregation of clinical and pathological data from two major hospitals

in Lombardy: Papa Giovanni XXIII Hospital in Bergamo and Ospedale di Circolo in Varese. Jointly, the Plastic Surgery Departments of these two centers provide related healthcare to nearly 2 million people, representing 20% of Lombardy population. The cities of Bergamo and Varese were also particularly fitting to the purpose of this study, since they represent the worst-hit areas during the pandemic's so-called first and second wave, respectively.

The first and foremost information we acquired was that the NMSCs that we excised after the pandemic outbreak were significantly larger in size (+9.4 mm, $p < 0.0001$) than those we operated before COVID-19 reached Italy. This increase was significant even when we separated cSCCs (+10.3 mm, $p < 0.05$) from BCCs (+6.1 mm, $p < 0.05$). Despite these findings, we found no significant difference in incomplete excisions between the two bimesters (11.9% versus 10%). Since Bergamo and Varese surgical teams did not change, we can assume that the expertise of surgeons overcame the challenge of more local advanced cancers.

Several studies reported that since the pandemic outbreak fewer patients are undergoing screenings, leading to fewer and less prompt cancer diagnoses¹⁹⁻²¹, as well as a delay in medical^{22,23} and surgical treatment²⁴ of previously diagnosed cancers. The natural consequence is that cancer presents at a later stage and often requires more complex care.²⁵ On this matter, Valenti et al. already reported a significant increase in the incidence of "advanced" NMSC, when comparing data from pre-lockdown and post-lockdown periods. They also registered a delay in dermatologic follow-up visits and hypothesized a causal relationship between the two phenomena.²⁶ As distinct from Valenti paper, in this study, we firstly assessed the objective parameter of cancer size, then we evaluated the factors that could have determined its variation; finally, we paraphrased these factors in four consecutive steps.

The *first step* is the moment when the patient notices the lesion and considers it worthy of medical evaluation. The *second step* corresponds to the dermatologist evaluation, which requires a general practitioner's prescription and is necessary to set the indication for surgical removal and histological analysis. Only lesions that involve high aesthetic value sites (i.e., the face) and/or require more complex reconstruction are referred by the dermatologist to the plastic surgeon, who provides the patient's admission on the surgical waiting list (*third step*). The *fourth* and last *step* is surgery, which happens after a time span that depends on: (i) the urgency of removal (based on suspected diagnosis, dimensions, proximity to noble structures, and high risk of disfiguring sequelae); (ii) number of enlisted patients that are classified with the same priority; and (iii) availability of operating rooms and health personnel.

We observed that patients who underwent surgery in December 2020 and January 2021 waited on average 6.3 less days from the moment of booking to the evaluation visit with the plastic surgeon (third step), and 17.6 less days from the aforementioned visit to surgery (fourth step), when compared with the ones that were operated in the same bimester pre-COVID-19. These results frankly clash with the low available resources (operating rooms and personnel) during pandemic. The reason lies in the National and Regional Health System decision to give priority to the most aggressive/urgent pathologies; consequently, the waiting

list for all other diseases (i.e., second-stage breast surgery) was temporarily *frozen*. Moreover, both Plastic Surgery Departments in Bergamo and Varese started classifying and prioritizing "urgent" cancers according to the following main criteria: (i) dangerous anatomical site (such as the face); (ii) large dimensions; and (iii) suspicion of more aggressive tumor (i.e., cSCC). Data confirm this forced choice: we witnessed, in the post-COVID-19 bimester, a significant ($p < 0.05$) increase in cutaneous SCC diagnoses with constant (67.1% versus 70%) percentages of lesions situated in the face.

Proceeding backward in our chronological sequence, we considered the time between when a patient books the dermatological visit and when he is actually evaluated, that is, the "second step". According to the abovementioned urgent referral system, patients with aggressive cancer were visited at a suitable time.

Because we ruled out the factors related to the "healthcare waiting list" (i.e., from fourth to second step), by process of elimination, we can assume that the reason underlying the lesions' enlargement relies in "step one", which refers to patient-related variables. Common factors associated with longer "patient delay" in NMSC diagnosis are as follows: (i) age ≥ 65 ; (ii) not easily visible site; (iii) tumor arising on a chronic lesion; (iv) absence of symptoms, and (v) no family/personal history of NMSC.^{27,28} In our series, both age and body location do not show any significant difference between the two evaluated periods, and we have no reason to believe that any of the other features changed. As some upcoming studies in other branches of oncology are pointing out, individuals experiencing non-cancer-specific symptoms often postpone seeking examination and treatment.^{29,30} Nonetheless, both the anxiety of catching the COVID-19 disease in a healthcare environment^{29,30} and the moral concern of wasting the practitioner's time or healthcare scarce resources³¹ restrained patients to have a clinical diagnosis. Consequently, we must consider that the COVID-19 pandemic itself might be accountable for the delayed diagnosis of NMSC. This has a remarkable bearing on patients affected by skin cancer, who initially do not recognize it as a dangerous or pressing issue, therefore, do not feel the urge of seeking medical consultation and help for it.³²

Although this analysis apparently demonstrates that, after the COVID-19 outbreak, our hospitals were able to treat patients more rapidly, it exposes us to a constructive critique. During the pandemic, we witnessed a *funnel effect*: the shortage of operating rooms, personnel, and equipment forced us to mainly treat aggressive cancers and urgent diseases that benefited from *fast tracks*. The lesions that we classified as less alarming at the time of enlistment have been repeatedly down-shifted by higher-priority cancers and have been given time to progress into more aggressive cancers.

This dysfunctional scenario unfolds when urgent surgery becomes the rule, rather than the exception: a healthcare system whose time and resources are exhausted by high-priority lesions is inevitably headed to collapse. Although small NMSC mainly causes only local disease, its growth can result in significant tissue destruction and facial disfigurement, entailing not only major plastic surgery with serious psychological and functional consequences to the patient³³ but also longer surgical times and hospital stay. This trig-

gers a vicious cycle: operating rooms and hospital beds are saturated by the highest priority cases, whereas less alarming lesions are repeatedly postponed, the latter progressively worsen until they finally meet the “urgent criteria” and can eventually be treated. Additionally, surgery of all non-malignant pathology (i.e., second step breast reconstruction, oculo-palpebral and post-bariatric surgery, etc.), which by definition isn’t characterized by this worsening behavior, is indefinitely put on hold, with undeniable rebound on patients’ quality of life.

As a result of the anti-COVID-19 vaccination campaign, the pressure of the pandemic on hospitals is reducing, and the availability of operating rooms is gradually reaching full speed, as compared to pre-2020 standards. Further studies are needed to assess the long-term impact of the COVID-19 pandemic on the diagnosis and treatment of NMSC, as well as to confirm this trend whenever the COVID-19-related restrictions will be completely dismissed. In the forthcoming future, our primary goal is to clear the backlog of aggressive and harder-to-treat lesions as quickly as possible, in order to resume providing NMSC diagnosis and treatment earlier since its appearance.

Conclusions

The COVID-19 outbreak heavily impacted on the patients’ faculty to have their NMSCs promptly diagnosed and treated. Because of the restrictions imposed by the pandemic, all surgical capacity is absorbed by the most aggressive cancers, which are diagnosed and treated in a suitable time, thanks to the “fast-track” referral systems. Conversely, less-concerning lesions are left on hold, until they become advanced enough to be labeled as *urgent*. According to our results and discussion, it is paramount that Plastic Surgery Departments evade as soon as possible from this downward spiral. Unprecedented efforts - in terms of personnel, operating rooms, funding, and optimization of resources - should be made, in order to compensate for the pandemic-related delays. The waiting lists of urgent and soon-to-be urgent cancers must be swiftly cleared. Then, we will be able to treat patients affected by early-stage cancers promptly and with less demanding solutions (i.e., under local anesthesia, with shorter OR times and hospital stays). The desirable effect is to save resources and reinvest them in the treatment of *all* plastic surgery-requiring pathologies.

Ethical approval

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Declaration of Competing Interest

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