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EDITORIAL

COVID-19 STILL ON CENTER STAGE IN ONCOLOGY DEBATES

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The Covid-19 pandemic, which is still far from over, is continuing to take center stage in most debates on current cancer research and care. A year after Covid-19 outbreak and the first lockdown, it is clear that the disease had a heavy toll on cancer patients impacting on every stage from screening to diagnosis and treatment (1-3). With the availability of anti-SARS-CoV2 vaccines, recent debates focused also on the vaccination strategies for cancer patients and for those eligible to access oncology clinical trials (4, 5).

In our previous issue we discussed how the pandemic affected the number of new cancer diagnoses, showing a reduction compared to the same period in the preceding year (1, 6), and our authors presented some of the challenges faced from oncologists during the first wave of the pandemic (7, 8). In this issue of Annals of Research in Oncology, Lucia Fratino and Diego Serraino focus on some clear cut questions regarding SARS-CoV-2 infection, cancer, cancer therapies and immune suppression which demand attention and, possibly, guidelines, although recommendations for the management of cancer patients in the context of SARS-CoV-2 infection have been mostly produced outside the traditional “Evidence Based” benchmark because of the urgency (9). Luigi Cavanna and colleagues, who pioneered home treatment of Covid-19 patients, report in this issue on their successful experience in a Northern Italy area, which was heavily affected by the disease during the first wave (10). Cavanna and colleagues, defined as ‘heroes of the front lines’ by the Time (11), show how the early diagnosis and treatment of the infection in cancer patients could avoid hospitalization and death in their cohort, strongly suggesting that early home management and monitoring through telemedicine should be implemented (10).

Daniela Fanni and co-authors present a case of a 63-year-old patient affected by Covid-19 with progressive respiratory failure. Histological evidence allowed the diagnosis of pulmonary capillary hemangiomatosis (PCH), which reinforces the hypothesis that the endothelial dysfunction, capillary thrombosis and neoangiogenesis induced by SARS-CoV-2 infection could evolve toward PCH, leading to the disruption of lung architecture (12).

For the launch of Annals of Research in Oncology the chief editors, Antonio Giordano and Carmine Pinto, with the Edra Chief business and content officer Ludovico Baldessin, in collaboration with the Center for American Studies (https://centrostudiamericani...
nately, this cancer type often relapses requiring sec-
ondary cytoreduction surgery, so the authors investi-
gated whether the primary treatment could affect the
pattern of recurrent disease and secondary surgery. 
Their study suggests that the primary treatment, con-
sisting either of primary debulking surgery or neoad-
juvant chemotherapy followed by interval debulking
surgery, should be considered among the selection
variables for secondary cytoreduction surgery further
implementing other parameters such as clinical score
based on ascites, performance status, and absence of
residual disease upon primary surgery (13).

Lucia Mangone and colleagues present in this issue
data from the Italian Association of Cancer Regis-
tries (AIRTUM Working Group) on the epidemiol-
y of neuroendocrine neoplasms (NEN) in Italy. 
The authors collected data from thirty-eight cancer
registries spanning the 1976-2012 period concern-
ing a total of 9,707 NENs. The study showed that
the incidence of NENs increased almost sevenfold
since 1976 and a fifth of all cases showed an asso-
ciation with another cancer, which might affect
clinical management decision strategies (14).

Alessandro Lambiase and colleagues review the
latest advancements in the classification and treat-
ment of ocular surface tumors, which include a
range of lesions involving the conjunctiva and cor-
ea, ranging from benign lesions to life-threatening
malignancies. The authors report recent evidence
that topical chemotherapy has been showing com-
plete tumor resolution and a low recurrence rate
with less injury compared to surgical removal (15).

Finally, we asked Massimo Di Maio, Professor of
Medical Oncology and Secretary of the Italian Asso-
ciation of Medical Oncology, AIOM, to comment on
the value of health-related quality of life (QoL) and
patient-reported outcomes (PROs) in oncology clin-
cial trials (17). The article, written in a question &
answer, interview format, will provide readers with
a timely overview on the crucial need to implement
clinical trials with both QoL assessment and PROs
along with methodological steps that will help us to
inch closer to a more patient-centered approach.
REFERENCES


EDITORIAL

SARS-CoV-2 AND ONCOLOGY

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KEY WORDS
SARS-CoV-2; COVID-19; Oncology; research; impact.

IMPACT STATEMENT
This paper discusses open questions posed by the disruption of health systems—with focus on cancer—caused by the SARS-CoV-2 pandemic.

The impact of infection with the severe acute respiratory syndrome 2 (SARS-CoV-2) coronavirus, and the subsequent illness COVID-19, on people who suffer from neoplastic diseases remains one of the crucial health issues in the COVID-19 era. Its importance has been well recognized and evaluated since the early phase of the pandemic (1). As of March 2021, more than 10,000 articles have been published in the medical literature with regard to the impact of SARS-CoV-2 infection in people with cancer (2). It is worth stressing that, worldwide, more than 15 million people are diagnosed with cancer every year, while about 50 million people are already living after a cancer diagnosis (3). How will COVID-19 modify the life of these individuals already living with cancer, and the life of the millions that will be diagnosed in the coming years?

The interruption caused by SARS-CoV-2 infection on health systems has led hospitals to suspend non urgent cancer diagnostic procedures and treatments, while cancer patients have been discouraged from seeking care at scheduled intervals. After one year in the pandemic and the starting of vaccine availability, the question of how long will the SARS-CoV-2 pandemic last and what effect will it have on primary (e.g., smoking, overweight, physical activity) and secondary prevention (i.e., screening), diagnosis, treatment and care of cancer patients is still looking for numerous answers. Available evidence is largely heterogenous, depending on two groups of factors. Biologic (e.g., immune depression related to anti-cancer treatments) and non-biologic factors (e.g., most people with cancer needs to interface with health institu-
Conversely, SARS-CoV-2 infection was documented among only 0.7% of 59989 Italian cancer patients undergoing active antitumor treatment according to the findings of a retrospective nation-wide study (5). Lack of excess of SARS-CoV-2 infection has been documented in a clinical cohort of 1.016 patients with cancer history in Austria. Only four of them (0.4%) turned out to be have acquired SARS-CoV-2 infection, a proportion comparable to that measured among non-cancer patients (7). Other investigations have indirectly assessed the prevalence of SARS-CoV-2 infection by estimating the proportion of cancer patients among examined people. For instance, 6%-7% of COVID-19 patients hospitalized in New York turned out to be cancer patients, a proportion higher than expected according to cancer prevalence in the corresponding general population (8, 9).

Adverse outcomes and increased risk of death have been already documented in cancer patients with SARS-CoV-2 infection (10-12). A pooled analysis of 52 studies published as of July 2020 estimated a high probability of death for infected cancer patients, with a case fatality rate of 25.6% (13). Findings from an international cohort study identified factors associated with an increased risk of 30-day mortality, including ageing, male sex, smoking and the presence of comorbidities (14). Among 1.004 cancer patients enrolled in the UK Coronavirus Cancer Monitoring Project, the all-cause risk of death in cancer patients with SARS-CoV-2 infection was associated with increasing age, and was particularly elevated in patients with hematological malignancies, a 2.25 fold increase for patients with leukemia, and a 2.09 fold increase for those hematological patients treated with chemotherapy (10). It has also been estimated that the COVID-19 diagnostic delay in the United Kingdom could cause in the next 5 years up to a 9.6% increased in death rate for breast cancer, 16.6% for colon-rectal cancer, 5.3% for lung cancer and 6.0% for esophageal cancer (12). In northern Italy, adverse outcomes, including death, were significantly more elevated in persons with SARS-CoV-2 infection and cancer than in persons with SARS-CoV-2 infection without cancer (4, 15).

Based on ongoing evidence, guidelines have been promptly circulated by scientific associations, including the European Society of Medical Oncology (ESMO) (16). Similar documents were issued in Italy for the management of cancer patients in the COVID-19 era by the medical community (17-19).
The COVID-19 pandemic has thus urged the cancer community to envisage a hardly hypothesized scenario – the presence of a new actor in the cancer drama- that pose unexpected challenges to public health, cancer patients, clinicians and researchers. The numerous studies already published on the relationships between COVID-19 and cancer have undoubtedly helped to focus major questions and immediate solutions. To further limit the disruption to cancer care caused by the COVID-19 pandemic, the persistence of scientific research at the pace of the one carried out in the first year of the pandemic will be of utmost importance.

**ETHICS**

**Fundings**

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**Conflict of interests**

The authors have declared no conflict of interests.

**Authors’ contribution**

All the authors contributed equally to conception, data collection, analysis and writing of this paper.
REFERENCES

ABSTRACT

Epithelial Ovarian cancer is the most lethal and silent gynaecological tumor and relapses in about 75% of cases. Retrospective data supported the superiority of secondary cytoreduction surgery (SCS) plus chemotherapy versus chemotherapy alone; in order to best select patients for SCS literature established a clinical score based on ascites, performance status, and absence of residual disease to primary surgery. The present study analyzed the outcomes and pattern of relapse of a population with first relapse of ovarian cancer undergoing secondary surgery without residual tumor divided into two groups based on the type of treatment at the first diagnosis (primary debulking surgery [PDS] or neoadjuvant chemotherapy followed by interval debulking surgery [IDS]). This is an observational retrospective study carried out at the referred Centre of Oncologic Gynaecology of Bologna, Italy on patients who underwent SCS for ovarian cancer between January 2009 and December 2019 retrieved in an electronic database. Clinical surgical and pathological data were analyzed. Data about time and pattern of relapse and overall survival were evaluated. Out of 270 ovarian cancer patients, 69 were enrolled in the study; 49 patients who at first received primary surgery (Group 1) and 20 patients at first received interval surgery (Group 2). The 5-year
In patients with advanced epithelial ovarian cancer, primary treatment impacted among the selection variables for secondary cytoreduction surgery and primary debulking surgery reported better outcomes.

**KEY WORDS**
Ovarian cancer; secondary surgery; interval debulking surgery; primary debulking surgery; recurrence.

**INTRODUCTION**
Epithelial ovarian cancer (EOC) is a relatively rare disease with the highest incidence rates in western countries such as Europe and North America (8 cases per 100,000). This cancer is the most lethal and silent gynaecological tumor with diagnosis in advanced stages (III-IV) in about 80% of cases and a five-year survival of only 20-30% (1, 2). The standard approach is surgical cytoreduction and chemotherapy with platinum and taxane compounds (3–7). Surgery can be offered at diagnosis (primary debulking surgery, PDS) or after neoadjuvant chemotherapy (NACT) (interval debulking surgery, IDS), with the goal to obtain absent or minimal residual disease and optimal debulking surgery represents one of the major prognostic factors (4). Despite optimal surgery and appropriate chemotherapy, about 70%-80% of patients will develop recurrence that results in about 23% within 6 months, and 60% after 6 months to the last platinum administration. Based on these parameters, patients were defined platinum sensitive and platinum resistant (8, 9).

When disease relapse occurs, surgery is a possible option in platinum sensitive patients with the same objective of primary surgery: minimal or absent residual disease. Some retrospective data supported the superiority of secondary cytoreduction surgery (SCS) plus chemotherapy versus chemotherapy alone (10), however the use of SCS is controversial. Some Authors have reported that the improved outcomes may reflect selection bias rather than the superiority of SCS due to the retrospective design of the studies. Some selection biases were explained by Gockely A et al. in 2019 (11) in a large retrospective study. They found that patients who underwent SCS were younger (p = 0.001), with an earlier stage disease at diagnosis (p = 0.002) and longer disease-free intervals (p < 0.001), compared with those taking chemotherapy alone, no significant differences in complication rates were found between patients receiving SCS versus those having chemotherapy only. According to the sensitivity analysis performed in the study, the survival benefit related to SCS could be explained by a lower incidence of multiple sites of relapse, ascites or carcinomatosis among women undergoing SCS.

The consensus of scientific community recognized that patients with the best outcomes were those submitted to SCS with minimal or absent residual disease and with long disease-free interval after adjuvant therapy (> 6-12 months) (12-15). In order to best select patients for SCS, European Researchers established in the AGO-DESKTOP studies designed and applied a clinical score for SCS (Arbeitsgemeinschaft Gynaekologische Onkologie, AGO score) (16): ascites < 500 ml, patients’ performance status, absent residual disease to primary surgery. Presence of unresectable disease to imaging, contraindications to surgery and possibility to complete cytoreduction were also take into account. Recently, two randomized studies were published reporting different outcomes. In 2019, the GOG 213 randomized trial published in the New Eng-
land Journal of Medicine failed to demonstrate a surgery-determined advantage in both Progression Free Survival (PFS) and Overall Survival (OS) in recurrent ovarian cancer versus chemotherapy alone (17). Conversely, after one year, final analysis from the AGO DESKTOP III/ENGOT-ov20 study looking at the impact of SCS in recurrent ovarian reported a median of 16 months longer survival in around 75% of patients that had a complete resection respect to patients who did not receive surgery (18).

From an evaluation of the studies proposed in the literature, among the parameters used in the decision for secondary surgery, PDS adjuvant chemotherapy or neoadjuvant plus IDS were the types of treatment at diagnosis that were not considered. It is known that patients who undergo neoadjuvant chemotherapy and IDS are characterized by higher burden disease, selection of chemorestant clone by drugs administered, different pattern of relapse respect to PDS and adjuvant chemotherapy (19).

The association of results derived from PDS or IDS can lead to an incorrect analysis, risking to unify data that concern two different histories of disease and with different outcomes.

The main aim of the present study is to analyze the outcomes of a population with first relapse of EOC undergoing SCS divided into two groups based on the type of treatment at the first diagnosis (PDS or IDS). Further evaluations will be the pattern of relapse (abdominal, extra-abdominal, single or multiple peritoneal, lymph node, hepatic, pelvic) and the incidence of post-surgical complications between two groups.

**MATERIALS AND METHODS**

This is an observational retrospective study carried out at the referred Centre of Oncologic Gynaecology of Bologna, Italy on patients who underwent SCS for ovarian cancer between January 2009 and December 2019 retrieved in an electronic database. Design of the study was reported in figure 1a. The study is part of a larger study that was approved by local Ethical Committee.

Inclusion criteria were: EOC according to the WHO criteria, patients older than 18 years old, FIGO (International Federation of Gynaecology and Obstetrics) Stage III-IV, PDS or IDS with no residual macroscopic disease, SCS without residual macroscopic disease, follow up data after SCS at least six months. Exclusion criteria were: borderline and no epithelial ovarian cancer, Stage FIGO at diagnosis I-II, Patients stage III-IV with no resected disease, residual macroscopic disease at first diagnosis, recurrent disease treated with chemotherapy; missing data about follow-up or surgical primary/secondary treatments, other neoplasia in the last 5 years.

Patients were divided into two groups: Group 1 includes patients with first relapse EOC submitted to SCS after PDS at first treatment; Group 2 includes patients with first relapse submitted to SCS after IDS at first treatment. At the time of the first diagnosis the decision-making process on whether to refer patients to PDS or NACT was taken after diagnostic laparoscopy by the two senior surgeons, to avoid selection bias.

Selection criteria for SCS were: AGO score (16) positive, imaging evaluation (computer tomography, CT or 18F-FDG PET/CT) showed resected disease and possibility to complete cytoreduction. Otherwise, patients were submitted for chemotherapy without surgery selected according to the best treatment available. Patients scheduled for SCS were submitted to a diagnostic laparoscopy in order to confirm the surgical indication, if they were judged non cytoreducible to laparoscopy were selected for chemotherapy. Residual disease after surgery was classified in completeness of cytoreduction (CC): absence of disease (CC-0), minimal residual disease 0.1–0.5 cm (CC-1), and gross residual disease > 0.6–1.0 cm (CC-2) and > 1 cm (CC3). After surgery, patients were selected to receive chemotherapy with platinum and taxane compounds or other drugs based on oncologist evaluation, for a total of six cycles.

Follow-up was performed according to local guidelines of the hospital, in particular, physical examination, pelvic ultrasound, CA125 serum tumor marker (CA19-9 was tested only for mucinous tumors) CT scan were assessed every 4 months, 18F-FDG PET/CT was prescribed whenever there was a clinical suspicion of relapse or as confirmation of another instrumental examination such as CT. Planned follow up was modified, if required, according to patient's needs (suspect of relapse or request of clinical evaluation for symptoms).

Clinical and pathological data were collected and examined, including: age at diagnosis, body mass index (BMI), histological type, FIGO staging system (20), BRCA mutation if available, CA125 at recurrence, primary tumor treatment (surgery and/or chemotherapy), date of relapse, diagnosis meth-
Epithelial ovarian cancer stage III-IV

Primary Debulking Surgery (PDS)

No residual disease

First relapse

Secondary Cytoreductive Surgery (SCS) without residual disease

Group 1

Neoadjuvant chemotherapy

Interval Debulking Surgery (IDS)

Figure 1a. Shows the study design.

ods/system of relapse, site of relapse, date of relapse and secondary surgery, Aletti surgical complexity score (21), Peritoneal Cancer Index (PCI) (22), surgical complications (Dindo-Clavien classification) (23), other therapies performed in association with surgery (chemotherapy, radiotherapy), maintenance therapies, date of last follow-up, date of second relapse and date of death.

**Statistical analysis**

Standard descriptive statistics were used to evaluate the distribution of each variable. Continuous variables were reported as means ± standard deviation (SD) and categorical variables as frequencies or percentages. The distribution of variables between groups were compared with chi-square test or Fisher's exact test and Mann-Whitney U test or ANOVA test, as appropriate. Peri-operative complication rates were reported as the frequency and percentage of patients. All p-values reported are two-sided and a p-value < 0.05 was considered statistically significant. OS and PFS were estimated by the Kaplan-Meier method, and two groups survival curves were compared by the log-rank test.

OS, Post Relapse Disease Free Survival (PRDFS) and Post Relapse Overall Survival (PROS) were defined respectively as time in months from first diagnosis to last follow-up or death, months from first relapse diagnosis to second relapse or last follow-up, time from first relapse to last follow-up or death.

**RESULTS**

The recruitment flow chart is shown in figure 1b. Briefly, 760 patients with EOC (stage III-IV) undergoing surgical staging were retrieved in the database, of these patients, 344 (45%) received PDS (Group 1) and 416 (55%) neoadjuvant chemotherapy and IDS (Group 2). In Group 1, the percentage of patients receiving primary surgery without residual disease was 76% (263/344), and in Group 2 69% (196/283). Of these patients optimally cytoreducted, a total of 207 patients relapsed after a median of 22 months (range 6-76) and were evaluated for SCS. Sixty-nine (33%) patients met the inclusion criteria (AGO score combined to imaging evaluation) and were enrolled in the study, 49 out of 120 (40%) for Group 1, and 20 out of 87 (23%) for Group 2 (figure 1b). Of a total of 207 with first relapse, 138 (69%) were judged not amenable for surgery. Patients’ characteristics of the two groups are reported in table I. No differences were reported in age, BMI, stage, histology. Median of time relapse was shorter in Group 2, 28 months (range 12-67), respect to Group 1, 31 months (range 6-76), p = 0.05. BRCA status data are not available for all patients as BRCA mutation has been routinely checked in our Unit since 2015. A total of 49 (71%) patients in Group 1, and 14 (70%) in Group 2 were tested for mutations in BRCA genes. The mutation of both BRCA 1-2 genes was reported in 8 women (16%) of
Figure 1b. Shows the recruitment flow chart of the study with the number of patients evaluated and the patients excluded from our study population groups.

Table I. Clinical and pathological parameters of the study Population.

<table>
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<th>GROUP 1</th>
<th>GROUP 2</th>
<th>P &lt; 0.05</th>
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<tr>
<td>Total number</td>
<td>49</td>
<td>20</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>(range)</td>
<td>Median</td>
</tr>
<tr>
<td>Age</td>
<td>62</td>
<td>(24-83)</td>
<td>61</td>
</tr>
<tr>
<td>Age at the diagnosis</td>
<td>56</td>
<td>(19-76)</td>
<td>55</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>25</td>
<td>(15-39)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>FIGO Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>47</td>
<td>(96%)</td>
<td>18</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>(4%)</td>
<td>2</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
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<tr>
<td>Serous</td>
<td>37</td>
<td>(76%)</td>
<td>16</td>
</tr>
<tr>
<td>Endodermoid</td>
<td>9</td>
<td>(18%)</td>
<td>2</td>
</tr>
<tr>
<td>Mucinous</td>
<td>2</td>
<td>(4%)</td>
<td>1</td>
</tr>
<tr>
<td>Clear cell</td>
<td>1</td>
<td>(2%)</td>
<td>1</td>
</tr>
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N = number; BMI = Body mass index; FIGO = International Federation of Gynecology and Obstetrics.
Group 1 and in 7 (35%) of Group 2. In Group 1, 5 patients (10%) had the BRCA1 mutation, 3 (6%) had the BRCA2 mutation, 24 (49%) were not mutated, and 17 (35%) had BRCA unavailable status. In group 2, 6 patients (30%) had the BRCA1 mutation, 1 (5%) had the BRCA2 mutation, 7 (35%) were not mutated, and 6 (30%) had the BRCA unavailable status. Results about SCS are reported in Table II. The value of CA 125 was significantly higher in Group 2 respect to Group 1 (median 68 U/ml, range 12-304 versus 38 U/ml, range 2-375; p = 0.0206), the levels of CA 125 were significantly lower (p = 0.001) in the relapse than in the first diagnosis. The other parameters did not differ between two groups except for PCI than was higher in Group 2 without reaching significance (Table II). Surgical complexity (Aletti’s score) was significantly lower (p = 0.001) in the relapse than in primary surgery. There was no significant difference in post-surgical complication incidence between the two groups (Table II). The incidence grade 3 complications were reported in two patients in Group 1 and grade 4 in one patient in Group 2. A death was reported in Group 2 for myocardial ischemia. Pattern of first recurrence in both groups is reported in Figure 2. Lymph node recurrences and intraparenchymal metastasis was reported in both groups with no statistical significance, Group 2 relapsed more frequently as multifocal peritoneal disease (75%) respect to G1 (41%) (p = 0.02).

After SCS, both groups received systemic chemotherapy. In Group 1, 30 patients received chemo-therapy with carboplatin and gemcitabine, 19 patients with carboplatin and taxane. In Group 2, nine patients received carboplatin and gemcitabine, 11 patients with carboplatin and taxane. In Group 1, two of the patients that underwent surgery for thoracic relapse received radiotherapy in association to carboplatin and gemcitabine. Beside traditional chemotherapy, antiangiogenic drugs such as Bevacizumab and poly ADP-ribose polymerase inhibitors (PARPi) have been added. In Group 1, 33% (16/49) of patients received Bevacizumab and 20% (10/49) of patients received PARPi; of these, Olaparib was used in 5 patients with BRCA mutation and Niraparib in 5 patients with wild-type BRCA. In Group 2, 25% (5/20) of patients received Bevacizumab, 20% (4/20) received PARPi therapy, and 15% (3/20) received both therapies; in total 35% (7/20) of patients were treated with PARPi. Olapar-
disease combined to chemotherapy led to good prognosis (4, 24). This statement was translated to SCS and the favourable role of SCS on prognosis has been established for decades in retrospective studies and metanalysis (12, 17, 25) even if its effectiveness is closely related to a careful selection of patients to undergo surgery and more restrictive criteria about surgical complexity (AGO score) was applied to SCS. To confirm these data, two prospective randomized studies were proposed (GOG 213 and AGO-DESKTOP studies), however, opposite results were actually found. In 2019, results of one of the randomized studies, GOG 213, raised some concerns about the SCS survival improvement previously suggested. The study reported that SCS can be safely performed in these patients, but it did not improve overall survival. Some concerns about this study have been raised by European Scientists. The GOG 213 was designed to evaluate the impact of antiangiogenic treatment on OS in platinum-sensitive recurrent ovarian cancer (PSROC) and secondary aims were to explore the role of SCS; other bias reported were patient selection and the low percentage of CC-0 in the population analysed. Different results are reported from the second randomized study, DESKTOP III study, in which PSROC patients with positive AGO score reported an average increase of 5.6 months in progression-free survival (from 14.0

DISCUSSION
This is a pilot study performed in a selected population of recurrent EOC patients that, to our knowledge, is the first of its kind to investigate the impact of the primary treatment on the natural history of the disease. Here, we reported different outcomes between PDS and neoadjuvant and IDS patients in the pattern of relapse and PROS. Results reported that Group 1 was characterized by better prognosis and a more surgical favorable pattern of relapse. Surgery represented a cornerstone in the treatment of EOC, maximal surgical effort without residual

Figure 2. The figure shows the site and percentage of the pattern of relapse in our population study divided into the two study groups.
to 19.6 months) and a median survival greater than 16 months in approximately 75% of patients who had a complete cytoreduction compared to patients who received chemotherapy alone. The publication of SOLO 1 (26) study reporting a 3-year disease-free period due to target therapy with poly ADP ribose polymerase inhibitors (PARPi) in recurrent EOC BRCA-mutated patients raised further doubts about the role of SCS in these settings. Marchetti et al. (27) addressed this issue and subsequently reported a better OS in BRCA mutated patients undergoing SCS plus chemotherapy and PARPi compared to patients undergoing chemotherapy and PARPi alone (3-year PRS of 79% and 42%, p = 0.02). The results of Desktop III and the criticisms of GOG 213 have confirmed the indication to SCS even in the era of target therapy, such as PARPi. The key-points for a better prognosis for patients undergoing SCS were: patient’s selection and the absence of residual disease after surgery. Patients recruited in our study were strictly selected using AGO score criteria, the review of imaging CT and/or 18F-FDG PET/CT and finally diagnostic laparoscopy in order to confirm the first two parameters (figures 4, 5). With these modalities, our percentage of optimal debulking surgery was very high, 92% in Group 1 and 95% in Group 2. When comparing the two groups, a higher percentage of patients were scheduled for SCS in Group 1 (40%) respect to Group 2 (20%) associated to a better prognosis for the Group 1. Although both groups were without residual disease at the first surgery, the data seemed to indicate that another selection parameter could be the type of primary treatment. Based on these data and literature reports, it could be hypothesized that patients undergoing PDS who relapse but who have a positive AGO score are those who could obtain the greatest benefit from SCS if compared to the neoadjuvant group (Group 1). The reasons for this difference could be various. It could be the case that completely cytoreduced patients after NACT could have a higher incidence of residual microscopic lesions that are not surgically detectable because they are hidden by scar tissues, especially in the upper abdomen and diaphragmatic surfaces. Furthermore, after chemotherapy often whitish and flat areas are highlighted in the site of previous neoplastic nodules to which it is difficult to give a meaning: some theories suggest possible residual disease or outcomes of chemotherapy. After NACT, microscopic persistent neoplastic foci may contain chemotherapy-resistant clones. The process is directly proportional to the number of cycles, and

Figure 3. a. Kaplan–Meier curves of Overall Survival; b. Post Relapse Overall Survival; c. Post Relapse Overall Survival; in Group 1 (pink line) and Group 2 (blue line).
NACT could promote the selection of a major aggressive disease (17, 28).

On the other hand, no useful data are currently available to clarify whether and how the choice to administer PDS or NACT followed by IDS can change the natural history of recurrent ovarian cancer. However, some indications may be considered such as many authors discuss the benefits of surgery after more than 6 cycles of chemotherapy. Literature data indicate that the presence of a larger and heterogeneous tumour burden at the time of initiation of chemotherapy could play an important role in the development of drug resistance, thus leading some authors to speculate that avoiding PDS in favour of

Figure 4. $^{18}$F-FDG PET/CT image (4A) and surgical image (4B) show pararenal relapse of epithelial ovarian cancer (indicated by the arrows. * Liver; ** right kidney.

Figure 5. $^{18}$F-FDG PET/CT (5A) and surgical (5B-5C) image of two bowel relapses of epithelial ovarian cancer (larger lesion is indicated by the bold arrows, smaller lesion is indicated by the slim arrows). * Descending colon.
the pattern of relapse or level of CA 125 or PCI to recurrence. In support of this diversity we have found that the modalities of relapse are different between the two groups. The IDS group tends to relapse more frequently as multifocal or peritoneal disease (carcinosis) than the PDS group which has intraparenchymal and paucifocal relapses. The characteristics of Group 2 reduce the surgical indications and the chances of optimal surgery. This is confirmed by higher levels of CA 125 and the PCI in Group 2. Therefore, in our study we did not find a higher surgical complexity score or increased post-operative complications in Group 2. Our results are supported by the study of Petrillo et al. (29). Here, the author reports that the two different approaches widely used in advanced ovarian cancer, PDS and NACT followed by IDS, are associated with significant differences in terms of presentation of recurrent disease. Papers reported that patients who relapse after NACT often have widely disseminated carcinomatosis and experience a higher incidence of platinum resistance compared with those who recur after PDS. The limitations of our work are the small sample size and the retrospective nature of our study. Patient selection criteria for NACT and therapies have changed over time, however in our center, diagnostic laparoscopy has been widely used since its onset in patients with high tumor burden and we are one of the first institutions that used diagnostic laparoscopy to select ovarian cancer patients. And again, the lack of differences in clinical and pathological characteristics at diagnosis between the two groups, as well as the absence of residual tumour after PDS and IDS, make the two series homogeneous and comparable. Biological genetics or biological components were not taken into account and this could be a bias of the study.

CONCLUSIONS
In conclusion, our study lays the foundation for considering the primary treatment received by patients among the selection variables for SCS. Relapse after PDS results in a more favourable pattern of recurrent disease and SCS after PDS offers longer survival if pre-existing criteria are selected (AGO scoring criteria) and diagnostic laparoscopy is performed. Certainly, further evaluations are needed to confirm our data and to clarify the impact of PDS and NACT on the natural history of ovarian cancer. However, it must be considered that the decision for the neoadjuvant must be the result of a careful evaluation and must be made in referral Centers in order not to reduce future surgical chances of patients with a disease where relapse occurs in about 75% of patients in the advanced stage.

ETHICS
Fundings
There were no institutional or private fundings for this article.

Conflict of interests
The authors have declared no conflict of interests.

Availability of data and material
The data underlying this article can be shared just before a reasonable request to the corresponding author.

Code availability
N/A

Authors’ contribution
AMP: writing original article, formal analysis; MT: investigation; EDC: conceptualization; CAC: data collection; AB: visualization; SB: software; GD: data collection; SG: supervision; PDI: supervision.

Ethical approval and consent to participate
The study is part of a larger study that was approved by local Ethical Committee (number 160/2012/O/Sper).
REFERENCES


19. Gadducci A, Cosio S, Zizioli V, et al. Patterns of Recurrence and Clinical Outcome of Patients With Stage IIC to Stage IV Epithelial Ovarian Cancer in Complete Response After Primary Debunking
ABSTRACT

Neuroendocrine neoplasms (NENs) account for 0.5% of all neoplasms worldwide. The aim of the study was to describe the epidemiology of NENs in Italy and the association with a second neoplasm using the Italian Cancer Registries (AIRTUM) database. Thirty-eight cancer registries were involved in this study in the period 1976-2012. The standardized incidence rates and the relative 5-year survival are reported. Cases by site, sex, and age, and the second cancers associated with patients with NENs are described.

A total of 9,707 NENs were reported to the AIRTUM database: 5,318 males (54.8%) and 4,389 females (45.2%). Lung and small intestine were the most frequent sites in both sexes. The standardized incidence increased from 1 case per 100,000/year (1976) to 5.46 case per 100,000/year in 2010 (95% CI 4.90-6.06), with a significant difference between rates in males (6.51, 95% CI 5.61-7.51) and in females (4.60, 95 CI 3.91-5.37). Incidence increased gradually in both sexes up to age 40-45, after which it increased rapidly. The 5-year relative survival was 59.7% (53.9% in males and 66.5% in females). NEN patients had a slight, not significant excess risk of having a second tumour: standardized incidence ratio 1.06 (95% CI 0.98-1.15). Of the 9,707 NENs studied, 2,033 (21%) had a second neoplasm: among these, 29 were NENs, 1,360 were other previous tumours, and 644 were other following tumours (78 synchronous and 566 metachronous tumours).

Although traditionally thought to be rare, incidence has increased by nearly sevenfold since 1976. Differences in registration accuracy and classification criteria challenge comparisons between areas and time.
INTRODUCTION

Neuroendocrine neoplasms (NENs) are tumours that originate in neuroendocrine cell compartments localized in numerous different organ systems. These tumours are most frequently found in the gastrointestinal tract and the bronchopulmonary system (1), reflecting the density of neuroendocrine cells in these tissues. There is, however, a portion of unknown primary origin (UPO) NENs, which are advanced neoplasms constituting 11-22% of all NENs; by definition, their primary tissue of origin has not been identified with standard diagnostic work-up (2). Delineating the primary site of origin of UPO-NENs has important implications for selecting the appropriate treatment and overall prognosis.

NENs account for about 0.5% of all neoplasms worldwide and are characterized by their ability to produce peptides that sometimes cause peculiar hormonal syndromes (3). Several studies (the United States, the Netherlands, and the United Kingdom) have described the incidence of NENs and the race, sex, and primary tumour site distributions and survival duration (1, 4-6). Despite the passage of almost a century, the classification of NENs is still under debate. This reflects the morphological and biological heterogeneity of these lesions and the advances that have been made in both cellular and molecular biology (7). In particular, a significant number of NENs in the general population are not classified using the ICD-O-3 codes associated with carcinoid tumours (8240-8246 and 8249) (8). The 2010 WHO classification for gastroenteropancreatic NENs introduced a grading system based on mitotic count and Ki-67 proliferation index according to the ENETS scheme (9-10). In 2018, WHO published a uniform classification framework for all NENs based on the distinction between well-differentiated neuroendocrine tumours (NENs) and poorly differentiated neuroendocrine carcinomas (NECs); the latter share with NETs the expression of neuroendocrine markers but are different from a genetic, histological, and predictive point of view (11). The current 2019 WHO classification of digestive system NETs grades tumours as G1, G2, or G3 on the basis of proliferation activity as assessed by mitotic rate and Ki67 proliferation index. They are morphologically distinct from NECs, whose subtypes are small cell NEC and large cell NEC (12). The 2020 WHO classification for neuroendocrine neoplasia of female genital tract is still largely based on the 2018 WHO version as other organs will be in the next classifications (13). NENs have in general been considered indolent tumours with low metastatic potential. However, some NEN subtypes are highly malignant and have a bad prognosis as they are resistant to therapy (1). Incidence is increasing but it is unclear whether this trend is due to an increased awareness among physicians, to improved diagnostic tools, or to an actual increase in NENs incidence (7).

The aim of this study was to describe the incidence and survival of NENs in Italy and a possible association with second neoplasm, using the AIRTUM (Italian Association of Cancer Registries) database.

MATERIALS AND METHODS

Cancer registries and data source

Thirty-eight Italian cancer registries (CR) participated in the study, sending their data to the AIRTUM database. Data include both tumour characteristics and patient information, and in 2019, covered approximately 70% of the total Italian population. The dataset contained more than 3,000,000 neoplasms (all tumours) diagnosed between 1976 and 2015 but this study includes 9,707 cases of NENs diagnosed only in the years 1976-2010, because data for the subsequent period were not complete. The
Figure 1. List of 38 cancer registries* participating in the study and number of cases per year.
(*In italics are the cancer registries that have merged in recent years).

Figure 2. EU standardized incidence rates for 100,000 years/person. Years 1976-2010.
cancer registries included throughout the study period varied; they are described in figure 1. ICD-O-3 histology codes were used to identify NENs, which includes (table 1): islet cell carcinoma, insulinoma, glucagonoma, gastrinoma, mixed islet-cell/exocrine adenocarcinoma, vipoma, somatostatinoma, enteroglucagonoma, carcinoid, enterochromaffin cell carcinoid, enterochromaffin-like cell tumours, goblet cell carcinoid, composite carcinoid, adenocarcinoid, neuroendocrine carcinoma, and atypical carcinoid. Small cell and large cell neuroendocrine carcinoma of the lung, pheomochromocytoma, paraganglioma were excluded, as already proposed by Yao in 2008 (3). WHO classification based on grading was not routinely available in cancer registries during the period under study.

Statistics
We have reported cases by site and sex. The incidence rate per 100,000 population per year, standardized on the European population 2013, was calculated from 1976 to 2010 because 2011-2012 included data from only one CR. Age-specific rates were calculated over the whole period 1976-2012 per 1,000,000 to better distinguish between trends in males and females.

The 5-year relative survival, with relative 95% CI, was calculated using the actuarial method (14).Second tumours were calculated by crossing the NENs with all the tumours in the database and evaluating the second tumours before or after a diagnosis of NENs. The latter were termed synchronous if they arose within two months of diagnosis or metachronous if they occurred 2 months after a diagnosis of NEN. Standardized incidence ratio for all cancer sites except non-melanoma skin cancers was computed using age groups of 10-year specific rates to compare the incidence of second cancers after the diagnosis of a NEN with the expected number of cancers in a similar population according to the age-specific incidence for all sites observed in Italy for the same period.

RESULTS
Between 1976 and 2012, a total of 9,707 NENs were reported to the AIRTUM database: 5,318 males (54.8%) and 4,389 females (45.2%). Lung (35.8%), small intestine (16%), and pancreas (10.2%) were the most frequent sites in males, while lung (29.6%), small intestine (12.8%), and colon (12.1%) were the most frequent sites in females (table II). Of the colon cancers, 302 cases were located in the appendix site (C18.1), mostly NOS (not otherwise specified) carcinoids.

The standardized incidence rate calculated on all the cases was equal to 1.97/100,000/year but with a great variability by sex and by period. In fact, the trend of NENs in Italy has gradually increased since the 1980s, going from a rate of 1 case per 100,000 to over 5 cases per 100,000 in recent years (figure 2), more so for code 8246.3 (neuroendocrine carcinoma) than for 8240.3 (carcinoid). In 2010, the last available year, the rate was 5.46 (95% CI 4.90-6.06), with a significant difference between males (SIR 6.51, 95% CI 5.61-7.51) and females (SIR 4.60, 95% CI 3.91-5.37) (table III). Concerning age, the incidence increased gradually in both sexes up to age 40-45, after which it increased rapidly especially in males, where it reached 8 cases per 100,000; in females it reached 6 cases per 100,000, then decreased in both sexes from age 75 on (figure 3). The 5-year relative survival, referred to the period 1976-2010 with follow-up to 2015, was 59.7% (95% CI 58.5-60.9): 53.9% in males and 66.5% in females. Of the 9,707 NENs studied, 2,033 (21%) had a second neoplasm: of these, 29 were NENs, 1,360 other previous cancers, and 644 were other following tumour (78 synchronous and 566 metachronous tumours) (figure 4). Of the 78 synchronous cases, the majority were lung (15 cases), colon (11 cases), prostate, kidney, and thyroid (6 cases). Of the 566 metachronous tumours, the most frequent sites (excluding skin) were prostate (71), breast (51), colon (48) lung (44), and bladder (36) (table IV). The multivariate analysis shows that overall, patients with NEN had a slight, not significant excess risk of having a second tumour (SIR 1.06, 95% CI 0.98-1.15).

DISCUSSION
The epidemiology of NEN in Italy has been described in a fragmentary way in studies on rare diseases (15) or as part of broader European studies (16, 17). In our study, the incidence of NENs in the last available year shows a rate of 5.46/100,000/year (95% CI 4.90-6.06), slightly higher than that reported by Trama(15) in the period 2000-2010: rate 4.15 (95% CI 4.06-4.23). The trends of NENs in Italy have shown a rapid increase, from 1 to over 5 per 100,000, similar to that reported by Yao in the US, where incidence increased from 1.09 in 1973 to
5.25/100,000 in 2004 (3), and in Northern Europe, where incidence increased from 2.35 per 100,000 in the period 1993-1997 to 4.6 per 100,000 in 2000-2004 (7). We cannot rule out that the advent of new diagnostic techniques, from CT to MR, from Octreoscan to Ga68 DOTA PET, from EUS to enteroclysis CT and video capsule, has greatly influenced the number of new diagnoses and consequently the incidence and time of survival. Another Italian study also reports this issue: cases diagnosed in the earlier period could be affected by a greater obsolete histological classification, while in more recent years, more sensitive classifications and imaging could guarantee greater diagnostic accuracy (18).

Lung and small intestine were the most common sites in Italy in both sexes, like in the US and Northern Europe (3, 7); however, we found a higher proportion of pancreatic tumours compared with these studies. It should be noted that all pancreatic cancers have shown a rapid increase in the Italian population in the last 10 years (19). In this study, instead, we observed fewer rectal cancers (5% in

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**Figure 3.** Specific incidence rates by age and sex per 1,000,000 person-years. Years 1976-2012.

**Figure 4.** Second tumours in patients with NENs. Years 1976-2012.

**Table I.** List of morphological codes included in this study.

<table>
<thead>
<tr>
<th>NENS</th>
<th>ICD-0-3 CODES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Islet cell carcinoma</td>
<td>8150/3</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>8151/3</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>8152/3</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>8153/3</td>
</tr>
<tr>
<td>Mixed islet-cell/exocrine adenocarcinoma</td>
<td>8154/3</td>
</tr>
<tr>
<td>Vipoma</td>
<td>8155/3</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>8156/3</td>
</tr>
<tr>
<td>Enteroglucagonoma</td>
<td>8157/3</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>8240/3</td>
</tr>
<tr>
<td>Enterochromaffin cell carcinoid</td>
<td>8241/3</td>
</tr>
<tr>
<td>Enterochromaffin-like cell tumours</td>
<td>8242/3</td>
</tr>
<tr>
<td>Goblet cell carcinoid</td>
<td>8243/3</td>
</tr>
<tr>
<td>Composite carcinoid</td>
<td>8244/3</td>
</tr>
<tr>
<td>Adenocarcinoid</td>
<td>8245/3</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>8246/3</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>8249/3</td>
</tr>
<tr>
<td>ICDO3</td>
<td>SITE</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>C00-C14</td>
<td>Oral cavity and pharynx</td>
</tr>
<tr>
<td>C15</td>
<td>Esophagus</td>
</tr>
<tr>
<td>C16</td>
<td>Stomach</td>
</tr>
<tr>
<td>C17</td>
<td>Small intestine</td>
</tr>
<tr>
<td>C18</td>
<td>Colon (including appendix)</td>
</tr>
<tr>
<td>C19</td>
<td>Rectosigmoid junction</td>
</tr>
<tr>
<td>C20</td>
<td>Rectum</td>
</tr>
<tr>
<td>C21</td>
<td>Anus and anal canal</td>
</tr>
<tr>
<td>C22</td>
<td>Liver-intrahepatic bile ducts</td>
</tr>
<tr>
<td>C23-24</td>
<td>Gallbladder-extrahepatic ducts</td>
</tr>
<tr>
<td>C25</td>
<td>Pancreas</td>
</tr>
<tr>
<td>C26</td>
<td>Other digestive organs</td>
</tr>
<tr>
<td>C30-31</td>
<td>Nasal cavity</td>
</tr>
<tr>
<td>C32-34</td>
<td>Lung</td>
</tr>
<tr>
<td>C37-39</td>
<td>Other intrathoracic organs (also thymus)</td>
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<tr>
<td>C40-41</td>
<td>Bone</td>
</tr>
<tr>
<td>C44</td>
<td>Skin</td>
</tr>
<tr>
<td>C47, C49</td>
<td>Soft tissue</td>
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<td>C70-C72</td>
<td>Brain</td>
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<tr>
<td>C74-C75</td>
<td>Adrenal and other endocrine glands</td>
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<tr>
<td>C76-77-C80</td>
<td>Unknown site</td>
</tr>
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<td>TOTAL</td>
<td></td>
</tr>
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</table>

Table II. Frequency of most common NENs, by site and sex. Years 1976-2012.

Italy, over 12% in the US, 7% in Northern Europe). It cannot be excluded that the Mediterranean diet, which is protective in terms of aggressiveness and stage of the disease, can also influence this tumour’s incidence (20).

The incidence by age confirms an increase in the adult-elderly population but a decrease in adults over age 75 years, and that males have a higher risk than do females (3). Five-year relative survival was 66.5% in females and 53.9 in males, similar to that seen in SEER (55%), NCR (50%), and Italian data (63%) (21), though referring to different periods. The median survival in our study was lower than that reported by Faggiano and colleagues in a large Italian case series, but they included a different mix of cancers due to using a different classification of NENs (18). The different survival, compared to other studies, could be linked to the fact that ours is a population-based study and therefore the heterogeneity of NENs and probably the lack of inclusion in the registry data of the subtypes associated with less biological aggressiveness (which are generally followed up in the outpatient setting and so are not registered in the Hospital Discharge Records system or in the pathology databases) may explain this lower survival. Furthermore, as our data refer to an earlier period (1976-2010), the impact of newly available effective treatments, even for metastatic cancer, has not yet been observed (22). In our study, NEN patients had a slight, not signif-

...
Table III. EU Standardized incidence of NEN by year and sex. Years 1976-2010.

<table>
<thead>
<tr>
<th>YEAR</th>
<th>MALES</th>
<th></th>
<th></th>
<th>FEMALES</th>
<th></th>
<th></th>
<th>ALL CASES</th>
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<tbody>
<tr>
<td></td>
<td>RATE</td>
<td>STANDARD ERROR</td>
<td>95% CI</td>
<td>RATE</td>
<td>STANDARD ERROR</td>
<td>95% CI</td>
<td>RATE</td>
<td>STANDARD ERROR</td>
<td>95% CI</td>
</tr>
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<td>1976</td>
<td>0.92</td>
<td>0.53</td>
<td>0.19</td>
<td>3.29</td>
<td>1.08</td>
<td>0.63</td>
<td>0.22</td>
<td>3.08</td>
<td>1.02</td>
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<tr>
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<td>0.01</td>
<td>2.75</td>
<td>0.27</td>
<td>0.27</td>
<td>0.01</td>
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<td>0.35</td>
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<td>0.04</td>
<td>1.65</td>
<td>0.31</td>
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<td>0.04</td>
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<td>0.00</td>
<td>0.94</td>
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<tr>
<td>1980</td>
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<td>0.42</td>
<td>3.18</td>
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<td>0.38</td>
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Table III. EU Standardized incidence of NEN by year and sex. Years 1976-2010.
veloped *metachronous* second cancers; in our study, the percentage was higher (6.6%). The increased risk of a second cancer following NEN could be due to several factors, including genetic, lifestyle, and/or treatment-related factors (29). Patients with familial NENs may also be more susceptible to developing cancer other than NEN (27). Also a small Irish study reported 14 second tumours among 46 patients with NENs: although the numbers are small, the follow-up of these patients needs to be optimized (30). Unfortunately, Italian cancer registries do not routinely report the NEN classification based on grade of differentiation, which is collected only for high-resolution studies. Furthermore, including data from the early 1970s means that only morphology and topography codes can be considered. Therefore, a more detailed comparison with the RITA or the RARECARE studies cannot be conducted (15, 16). Another limitation of our study is that we could not distinguish between cases occurring in patients with MEN-1 and in those with MEN-2 syndromes and other genetic endocrine syndromes (VHL, NF, SHD, and others). AIRTUM data based on ICD codes are not up to date with regard to the numerous subtypes of neuroendocrine tumours; functional NENs are underreported in many cancer registries and distinguishing between benign and malignant behaviour may thus be difficult. Analysing other comorbidities, such as obesity, hypertension, and diabetes, would also have been of interest, but this information is unfortunately not currently available in cancer registry databases. The study includes data from 38 cancer registries, which corresponds to around 30 million Italians, and spans a period of almost 40 years of registration, but geographic and temporal distributions are not homogenous. This heterogeneity among the registers in different periods could have affected our incidence trend estimate and did not allow us to study the trend of survival. Furthermore, there may be an underestimation linked to the fact that many tumours with neuroendocrine features might be under-reported in mortality certificates, *i.e.*, reporting “colon cancer” or “pancreatic adenocarcinoma” instead of their NENs counterparts.

### Table IV.
Second tumours (synchronous and metachronous) in patients with NEN diagnosis.

(*In italics are the cancer registries that have merged in recent years.*)

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**CONCLUSIONS**
In our study, the incidence of NENs in Italy was 5 per 100,000. Although traditionally thought to be rare, incidence has increased by nearly sevenfold since 1976. Five-year relative survival is 66.5% in females and 53.9 in males without any improvement over time. The occurrence of a second cancer was about 21%, with a slight, although not significant excess of risk. The availability of population-based data and second cancers associated with NENs could support clinicians in making the most appropriate choice for the management of patients with NENs.

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chiara M. Parma CR; Mangone L. Reggio Emilia CR; Carrozzi G. Modena CR; Ferretti S. Ferrara CR; Falcini F. Romagna CR; Caldarella A. Toscana CR; Vitarelli S. Macerata CR; Stracci F. Umbria CR; Iacovacci S. Latina CR; Ortolani R. Napoli Centro CR; D’Orsi G. Napoli Nord CR; Fusco M. Napoli Sud CR; Scala U. Salerno CR; Coviello E. Barletta-Andria-Trani CR; Quarta F. Lecce CR; Minerba S. Taranto CR; Sutera Sardo A. Catanzaro CR; Sciacca S. Catania-Messina–Enna CR; Vitale F. Palermo CR; Tumino R. Ragusa-Caltanissetta CR; Madeddu A. Siracusa CR; Candela G. Trapani-Agrigento CR; Cesaraccio R. Sassari CR).

ETHICS

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Conflict of interests

The authors have declared no conflict of interests.

Availability of data and material

All the data supporting the findings of this study are available within the article and can be shared just before a reasonable request to the corresponding author.

Authors’ contribution

LM: conceptualization, investigation, writing-original draft, visualization, supervision; CS: methodology; IB: writing - review & editing, supervision; PM: methodology; GC: conceptualization, supervision; PGR: conceptualization, writing-original draft, supervision. All authors have read and agreed to the published version of the manuscript.

Ethical approval

N/A
REFERENCES


NEW INSIGHTS ON THE DIAGNOSIS AND MANAGEMENT OF MALIGNANT TUMORS OF THE OCULAR SURFACE

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ABSTRACT
Tumors of the ocular surface encompass a wide spectrum of conditions involving the conjunctiva and cornea, ranging from benign lesions to life-threatening malignancies. These tumors are rare; however, they are commonly seen in the ophthalmological clinical practice as a group. The diagnosis of ocular surface tumors is mostly based on clinical evaluation of the conjunctiva and cornea and subsequent histologic confirmation. Recently, non-invasive diagnostic approaches including anterior segment high-resolution OCT (HR-OCT), showed promising results for their use as adjuvant for histology in case of suspicious lesions. The present review focused on the main malignant ocular surface tumors, including ocular surface squamous neoplasia (OSSN), melanocytic epithelial tumors, and conjunctival lymphoma, with the aim of discussing the epidemiological, clinical, and histopathological features, as well as to provide insights into classification and staging. In addition, the latest advances in the treatment of ocular surface tumors were reviewed, including the use of topical chemotherapy, which is gaining increasing acceptance over surgical tumor removal as it prevents surgery-related side effects and tumor recurrences.

KEY-WORDS
Ocular surface squamous neoplasia (OSSN); conjunctival melanoma; conjunctival lymphoma; anterior segment high-resolution OCT (HR-OCT); topical chemotherapy.

IMPACT STATEMENT
This review is aimed at providing clinical description of the main malignant ocular surface tumors along with recent advances in the diagnosis and treatment of these conditions.
INTRODUCTION

Tumors of the ocular surface encompass a broad spectrum of conditions involving the conjunctiva and cornea, and are classified based on site of origin into epithelial, stromal, caruncular, metastatic and secondary tumors (table I). Tumors of the ocular surface range from benign lesions such as conjunctival nevus, dermoid or squamous papilloma, to aggressive, life-threatening malignancies such as squamous cell carcinoma (SCC), lymphoma or melanoma (figures 1-3).

The conjunctiva is a mucous membrane which covers the back surface of the eyelid, the fornixes, and the anterior surface of the globe up to the corneo-scleral limbus. The conjunctiva is composed of a multilayered, non-keratinized epithelium and a stroma. Melanocytes are normally located in the basal layer of the conjunctival epithelium. The cornea is a clear, avascular structure that is composed of stratified, non-keratinized squamous epithelium, a stroma and a corneal endothelium. Melanocytes are described in the basal epithelial layer of the peripheral cornea, but they are absent in the central cornea. The corneo-scleral limbus represents the junction of the corneal and conjunctival epithelia. It contains the palisades of Vogt in which are located corneal stem cells. This region is also a common site for the development of corneal epithelial tumors (1). Ocular surface neoplasms arise from both epithelial and stromal structures; however, corneal stromal tumors are uncommon. Epithelial tumors of the ocular surface can be further subdivided in non-melanocytic or melanocytic (table II). The cornea is frequently invaded by tumors originating in the conjunctiva.

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Table I. Classification of tumors of the ocular surface. Modified from Grossniklaus et al. (4), Shields et al. (5) and Honavar et al. (6).

Figure 1. a, c. Bilateral conjunctival lymphoma, right eye. b, d. Left eye. a, b. Diffuse, slightly elevated, salmon-colored mass in the bulbar conjunctiva. Clinical appearance before. d, c. After systemic treatment.

Figure 2. a, b. Clinical aspect of two different conjunctival nevi showing intralesional cysts and feeder vessels.

Figure 3. Conjunctival melanoma. Pigmented, elevated, non-cystic mass with feeding and intrinsic vessels in the interpalpebral bulbar conjunctiva.
patients. They are thought to arise from the limbal stem cells, and most commonly occur in the interpalpebral region involving the bulbar conjunctiva and/or the cornea (9). They can be flat or raised, localized or diffuse, and may have surface keratin and feeder conjunctival vessels. They usually present as fleshy, placoid lesions with a gelatinous, leukoplakic, velvety or papilliform appearance, and may coexist with other ocular surface disorders. Nodular and diffuse morphological types are less common (10, 11). Of note, a diffuse appearance can simulate chronic conjunctivitis (12). When present at the cornea, they present as a flat opalescent layer (10, 11).

Histopathologic examination shows an invasive disease, characterized by malignant squamous cells crossing the basement membrane and growing in sheets or cords into the stromal tissue. Aggressive variants include spindle cell squamous carcinoma, mucoepidermoid carcinoma, and adenoid squamous cell carcinoma (10, 11).

Corneal and conjunctival squamous neoplasms can extend locally to invade the globe and orbit. These tumors can metastasize to regional lymph nodes with a reported incidence of less than 1%, but they are unlikely to metastasize systemically (13). According to the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) classification, OSSN is classified based on size and extent of involvement (14). Clinical factors such as tumor nasal location, involvement of the tarsal conjunctiva, presence of positive surgical margins, and high-grade lesions, have been associated with increased risk of recurrence (10, 11, 13).

Ocular surface squamous neoplasia

Ocular surface squamous neoplasia (OSSN) is the most common epithelial, non-melanocytic malignancy of the ocular surface. It involves neoplastic changes of the squamous epithelium of the cornea and conjunctiva, progressing from dysplasia to conjunctival intraepithelial neoplasia (CIN) (Tis: carcinoma in situ) and invasive SCC. Risk factors include ultraviolet (UV) light exposure, fair skin, infection with human papillomavirus (HPV), human immunodeficiency virus (HIV), prior skin cancer, older age (2–8).

OSSN lesions generally present as unilateral disease, but may be bilateral in immunosuppressed patients. They are thought to arise from the limbal stem cells, and most commonly occur in the interpalpebral region involving the bulbar conjunctiva and/or the cornea (9). They can be flat or raised, localized or diffuse, and may have surface keratin and feeder conjunctival vessels. They usually present as fleshy, placoid lesions with a gelatinous, leukoplakic, velvety or papilliform appearance, and may coexist with other ocular surface disorders. Nodular and diffuse morphological types are less common (10, 11). Of note, a diffuse appearance can simulate chronic conjunctivitis (12). When present at the cornea, they present as a flat opalescent layer (10, 11).

Histopathologic examination shows an invasive disease, characterized by malignant squamous cells crossing the basement membrane and growing in sheets or cords into the stromal tissue. Aggressive variants include spindle cell squamous carcinoma, mucoepidermoid carcinoma, and adenoid squamous cell carcinoma (10, 11).

Corneal involvement is characterized by loss of transparency and potential impairment of visual function. Conjunctiva and cornea allow for direct clinical evaluation, therefore, ocular surface tumors may be easily diagnosed, however, differentiating between benign and malignant ocular surface lesions, as well as among different malignant conditions, can be challenging for ophthalmologists and oncologists. Indeed, with the exception of tumor size, clinical features such as tumor location, keratinization, pigmentation, vascularization, and corneal invasion have not been associated with the likelihood of malignancy (1). Based on these observations, additional diagnostic exams and histopathologic confirmation after incisional or excisional biopsy are mandatory in the presence of suspected lesions. It is worth to note that an accurate and early diagnosis is critical, due to differences in the treatment and prognosis of these conditions.

**Table II. Classification of epithelial tumors of the ocular surface.**

Modified from Grossniklaus et al. (4), Shields et al. (5) and Honavar et al. (6).
Melanocytic epithelial tumors

Melanocytic epithelial lesions have similar histopathological and morphologic appearance to those of the skin, and include conjunctival nevus, complexion-associated melanosis (CAM), primary acquired melanosis (PAM) with or without atypia, and conjunctival melanoma (18). Conjunctival nevi are benign, circumscribed and typically pigmented lesions, although they may be amelanotic in rare cases. They can be congenital or acquired, and classically locate in the interpalpebral bulbar conjunctiva. They are flat to slightly raised, and usually contain clear cysts and feeder vessels. Importantly, the presence of internal cysts appears to denote a benign process. Similar to nevi of the skin, conjunctival nevi are categorized as junctional, compound, or subepithelial on histopathologic analysis. They can acquire pigment over time; however, the growth of conjunctival nevi is relatively stationary throughout life with an estimated risk of malignant transformation of less than 1% (10, 11, 19). Periodic observation is the management of choice. If the excision is performed for cosmesis or suspected growth, it is preferable not to leave any residual lesion (10, 11, 19).

CAM, also known as racial melanosis, is a benign conjunctival pigmentation commonly found in dark-skinned individuals and showing bilateral involvement. CAM is typically observed around the limbus and variably on the limbal cornea, and it appears flat and non-cystic on examination. Histopathological exams show the presence of benign melanocytes in the basal layer of the epithelium. There are studies demonstrating a mild increase in size with age; however, this condition has not been shown to progress to conjunctival melanoma. Periodic observation is advisable (10, 11, 20). PAM is an acquired, usually unilateral, pigmented condition, most likely occurring in fair-skinned individuals. It has been associated with neurofibromatosis, thus suggesting a possible origin from the neural crest (11). At examination it appears as a diffuse, flat, and non-cystic area of pigmentation, usually affecting the bulbar conjunctiva (10, 11, 19, 21). This aspect is to be related to the sole intraepithelial involvement of PAM compared to nevus. Moreover, the pigmentation in PAM may wax and wane over time. This condition has been classified in PAM with or without atypia based on nuclear features and growth pattern of melanocytes on histopathological evaluation. PAM with no atypia carries no risk for malignant melanoma progression, whereas risk rises to nearly 50% in PAM with atypia (10, 11, 19). PAM with atypia corresponds to melanoma in situ (Tis) in the AJCC-TNM classification of conjunctival melanoma (22, 23). Treatment is observation for PAM confined to less than 2 clock hours of conjunctival involvement. In case of PAM involving 2–5 clock hours of conjunctiva, the recommended treatment is surgical excision with cryotherapy to the margins. In case of PAM > 5 clock hours, the treatment of choice is wide incisional biopsy and cryotherapy to all remaining conjunctival pigmentation. As an alternative, application of topical mitomycin C (MMC) may be considered for treatment of diffuse or multifocal PAM (19, 21).

 Conjunctival melanoma is a rare tumor accounting for 2-5% of all ocular malignancies and 5-7% of all ocular melanomas, but it is among the most common malignant neoplasms of the ocular surface (24). In recent decades, the incidence of conjunctival melanoma has been increasing similar to cutaneous melanoma, while the incidence of uveal melanoma has remained relatively stable. This is thought to be related to the result of environmental exposure to UV light (25–27). Conjunctival melanoma mostly arises from PAM (53-75%), but can also arise from conjunctival nevi (18-30%) or de novo (5%) (21,24). Importantly, melanoma arising from PAM has been identified to have a higher risk of local recurrence. This tumor is composed of malignant melanocytes with polyhedral, spindle or epithelioid morphology, that violate the epithelial basement membrane on histopathological examination. These cells are positive for Bcl-2, S100, melanA, HMB45, from immunohistochemical studies. Detection of Ki-67 can be of value to assess biological behavior (24). This tumor typically affects elderly patients and presents as a pigmented and nodular lesion with prominent feeding and intrinsic vessels. The most common location is the bulbar conjunctiva near the limbus. Moreover, this tumor...
can be amelanotic or minimally pigmented in up to one-fifth of cases, possibly leading to diagnosis delay (21, 24). Conjunctival melanoma can cause distant metastases but also tends to extend locally. The AJCC clinical staging classifies melanomas based on degree of extension in the bulbar or non-bulbar conjunctiva, local invasion, regional lymph nodes or distant metastases (22, 23). Sentinel lymph node biopsy is recommended for staging of conjunctival melanomas, and should be especially considered in patients with tumors of more than 10 mm in diameter and 2 mm in thickness, non-limbal locations, and in the presence of tumor ulceration (23). The histopathological staging depends on tumor thickness and invasion of the substantia propria. Thickness of invasive tumor is classified as: ≤ 0.5 mm, 0.5-1.5 mm, and > 1.5 mm. Tumor depth does implicate greater risk for regional and distant metastasis and mortality (23, 28, 29). In addition, prevalence of epithelioid cells, local recurrence, and non-limbal locations, represent relevant negative prognostic factors (10, 11). At 10 years, local recurrence after therapy is estimated at 50-70% and distant metastases at 25% (11, 30–34). Similar to OSSN, the preferred treatment for conjunctival melanoma is complete surgical removal with cryotherapy to the margins. If margins are positive for invasive melanoma, repeated surgical treatment and adjuvant plaque brachytherapy, rather than adjuvant topical chemotherapy, should be performed (35–38). Local tumor recurrence is reported ranging between 18–35% with this approach (30, 39). Radiotherapy is also employed as an adjuvant in case of residual disease. Topical MMC is usually considered for recurrent conjunctival melanoma (21). Enucleation or orbital exenteration may be of choice in case of extensive tumors. Systemic chemotherapy is administered with combination of IFN and interleukin-2 in disseminated melanoma (40–43). Moreover, given the molecular and biological similarities to cutaneous melanoma, targeted therapies including BRAF inhibitors with or without MEK inhibition, and immune checkpoint inhibitors, have recently been investigated in a few case reports for treatment of conjunctival melanoma, with promising results (44).

**Stromal tumors**

Stromal tumors of the conjunctiva are rare and include benign and malignant conditions originating from various tissue elements such as vascular and lymphatic, fibrous, neural, histiocytic, myxoid, myogenic, and lipomatous tumors, and choristomas. Conjunctival lymphoma is the most frequent malignant stromal tumor of the conjunctiva. It can be primary conjunctival or develop as manifestation of coexisting systemic lymphoma. Approximately 5-15% of all extranodal lymphomas involve the ocular adnexa, and about 25% of these involve the conjunctiva (45–49). The most common subtype is low-grade extranodal marginal zone lymphoma, previously known as mucosa-associated lymphoid tissue (MALT) lymphoma, followed by follicular lymphoma, diffuse large B-cell lymphoma, and mantle cell lymphoma. Clinically, it presents as a diffuse, slightly elevated, salmon-colored mass, and it is mostly located in the bulbar conjunctiva and fornixes. (45, 47, 50). There is no clear clinical difference between conjunctival lymphoma and reactive lymphoid hyperplasia, the latter of which is benign. Therefore, biopsy is mandatory to establish a definite diagnosis (47, 51). On histopathological evaluation, conjunctival lymphoma is composed of subepithelial sheets of lymphocytes, and it is classified as reactive lymphoid hyperplasia or malignant lymphoma based on cells morphology and degree of differentiation. Furthermore, most are non-Hodgkin’s B-cell lymphomas, whereas Hodgkin’s B-cell lymphomas and T-cell lymphomas rarely affect the conjunctiva (10, 11, 47). It is classified according to the Ann Arbor staging system and the AJCC-TNM staging system for ocular adnexa lymphomas (OAL) (52). Importantly for this discussion, forniceal or midbulbar location, multifocality, and bilaterality are relevant prognostic factors for the development of systemic lymphoma. Low dose external beam radiotherapy (EBRT) is the treatment of choice for isolated conjunctival lymphoma or to the orbit including the conjunctiva. Five-year local control rate with radiotherapy alone in the treatment of conjunctival lymphoma ranges from 89 to 100%. In cases of bilateral involvement, systemic treatment is generally selected over bilateral EBRT (45, 48, 50).

**Caruncular tumors**

The caruncle is a peculiar region in the conjunctiva as it contains both mucous membranes and cutaneous structures. It is located in the medial canthus and it is composed of non-keratinized stratified squamous epithelium overlying a stroma of fibroblasts, melanocytes, sebaceous glands, hair follicles, and striated muscle fibers. Among caruncle tumors, nevus and papilloma are the most
Observation
For smaller lesions (≤ 4 clock hours limbal tumor or ≤ 15 mm basal dimension) that appear benign such as dermoid, or nevus, a diagnostic biopsy is usually not necessary. Periodic observation with slit-lamp photographs every 6 or 12 months looking for growth or malignant change is the optimal management of these conditions.

Surgical biopsy
Confirmation by histopathologic analysis on surgical biopsy is the gold standard for diagnosis. When a smaller tumor (≤ 4 clock hours limbal tumor or ≤ 15 mm basal dimension) does worth a biopsy, excisional biopsy is generally preferable over incisional biopsy. Among benign and malignant lesions to be treated with excisional biopsy are symptomatic dermoid, choristoma, steroid-resistant pyogenic granuloma, SCC, and conjunctival melanoma. Incisional biopsy is reserved for larger tumors (> 4 clock hour limbal tumor or > 15 mm basal dimension) that are symptomatic or suspected to be malignant. Examples include PAM, and large SCC. Also, for large or recurrent lesions, excisional biopsy leads to increased risks of limbal stem cell deficiency, symblepharon, and scarring, as well as requiring mucous membrane grafts from the contralateral conjunctiva, buccal mucosa, or amniotic membrane. Incisional biopsy is also appropriate for conditions that are rather managed with radiotherapy or chemotherapy, such as lymphoid tumors, conjunctival invasion by sebaceous gland carcinoma or metastatic tumors (10, 21). The use of incisional biopsy should be avoided for conjunctival melanoma, as this can increase the risk of tumor recurrence (30).

Cytology
Less invasive modalities including fine needle aspiration biopsy and impression cytology can provide useful information based on sampling of a few cells (1, 55, 56). However, these techniques have limited applicability due to the sampling of surface cells only, thus not allowing distinction of carcinoma in situ from infiltrating carcinoma.

Non-invasive diagnostic modalities
Non-invasive diagnostic approaches have been explored in recent years, and include in vivo confocal microscopy (IVCM), ultrasound biomicroscopy (UBM), and anterior segment high-resolution optical coherence tomography (HR-OCT) (1, 9, 57, 58).

Confocal microscopy (IVCM)
IVCM is an imaging method, which enables morphological and quantitative analysis of ocular surface structures and cells. It allows examination of tissue sections by selecting the depth of interest, and provides images of 1–2 μm lateral resolution and 5-10 μm axial resolution. The largest studies to date of IVCM for OSSN, conjunctival melanocytic lesions and lymphoma, demonstrated that IVCM cannot replace biopsy although it has some utility as an adjuvant for histology. (1, 57, 59).
Local excision with cryotherapy to the margins has been the mainstay treatment of ocular surface cancers, however, topical chemotherapy alone is now gaining increasing consensus among specialists in the field. Surgical removal has the advantage of serving as both as diagnostic and therapeutic procedure. However, surgery has potential disadvantages including limbal stem cell deficiency or conjunctival scarring, and it can leave residual disease leading to tumor recurrence (10,11,48).

Surgical techniques

Primary tumors of the ocular surface mostly arise in bulbar conjunctiva near the limbus. The treatment of choice for resection of limbal tumors is the ‘no touch, en-bloc tumor excision’ technique. This procedure involves excision of large margins with ‘en-bloc’ removal to avoid seeding of tumor cells. A conjunctival incision based at the limbus is made at least 4 mm outside the tumor margin. The incision is carried out through the episcleral plane, so that full thickness conjunctiva and Tenon’s fascia are included in the excised tissue. For any corneal involvement, application of absolute alcohol and then localized epitheliectomy 2 mm outside the corneal component is recommended. In advanced cases, lamellar corneal excision may be required for complete resection. If there is any scleral adhesion or corneal stroma involvement, a thin lamella of sclera is removed (0.2-0.3 mm depth), to achieve tumor-free margins and decrease the chance for tumor recurrence. Double freeze-thaw cryotherapy is usually performed to the borders of the remaining bulbar conjunctiva to eliminate subclinical tumor cells. It is not necessary to treat the corneal margins with cryoapplication. Limbal cryotherapy should be limited to 6 clock hours. The excision base is generally treated with absolute alcohol wash to avoid cryotherapy directly on the sclera. After this, conjunctival reconstruction should be performed with clean instruments to avoid tumor seeding (10,11).

Ultrasound biomicroscopy (UBM)

UBM is an ultrasound modality that uses a higher frequency transducer (35-100 MHz) than A-scan or B scan (10 MHz). This results in up to 20 µm axial and 50 µm lateral resolutions, and depth of tissue penetration of 4-5 mm. This technique has the ability to delineate tumor posterior margin and extent even in case of densely pigmented lesions or corneal opacities. This improves detection of tumor invasion, however, the resolution of intrallesional details is limited (1, 58).

Anterior segment high-resolution OCT (HR-OCT)

HR-OCT is non-invasive, non-contact device that provides cross-sectional images of the ocular surface with a resolution of 5 to 10 µm. Recently, the advent of ultra-high resolution (3-5 µm) OCT (UHR-OCT) using spectral-domain technology has enabled more detailed evaluation (60–62). HR-OCT is able to detect epithelial thickening and differentiating epithelial from subepithelial lesions of the conjunctiva and cornea (1, 9, 63). It can be used for OSSN detection in the presence of concomitant ocular surface disease, and in monitoring response to treatment. The classical findings of OSSN on HR-OCT consist of epithelial hyperreflectivity and thickening, and an abrupt transition between normal and cancerous epithelium (1, 63). Limitations of this technology for OSSN include difficulty in imaging the posterior border of thick, keratinized, and pigmented lesions due to shadowing of the image. HR-OCT can be helpful in differentiating between epithelial lesions of melanocytic origin, although it has the limitation of shadowing in densely pigmented lesions. For conjunctival nevi, this technique reveals intrinsic cysts even when they are not visible on clinical exam, as well as hyperreflective basal epithelial layers. In PAM, HR-OCT features are that of a uniform hyper-reflective band along the basal epithelium, with normal overlying epithelium and absence of cysts. However, HR-OCT is not able to evaluate atypia. For conjunctival melanoma, HR-OCT allows for detection of a hyper-reflective epithelium of variable thickening overlying a hyper-reflective sub-epithelial mass and absence of cysts. Also, HR-OCT has been studied in the diagnosis of conjunctival lymphoma, but it showed limitations including the inability to distinguish benign reactive lymphoid hyperplasia from conjunctival lymphoma, and poor detection of underlying tissues due to shadowing effect in case of thick lesions (1, 9, 58, 61–63).

Therapy

Local excision with cryotherapy to the margins has been the mainstay treatment of ocular surface cancers, however, topical chemotherapy alone is now gaining increasing consensus among specialists in the field. Surgical removal has the advantage of serving as both as diagnostic and therapeutic procedure. However, surgery has potential disadvantages including limbal stem cell deficiency or conjunctival scarring, and it can leave residual disease leading to tumor recurrence (10,11,48).
reveals tumor cells at the conjunctival margin, additional surgery or postoperative topical chemotherapy may be used.

Enucleation is reserved to patients with deep corneal or scleral tumor invasion or intraocular extension. Orbital exenteration is indicated in case of extensive tumor recurrences, non-resectable tumor without evidence of metastasis, or patients with painful eyes and unacceptable cosmesis. Before and during exenteration, the nasal lacrimal system should be evaluated for signs of disease. When the disease is exclusively conjunctival and/or orbital, a lid sparing exenteration can offer a socket to allow the placement of a prosthesis. Importantly, external beam radiotherapy (EBRT) can represent a valid alternative and/or adjunct to exenteration in cases with extensive palpebral, fornical, conjunctival, or caruncular involvement (10, 11, 16, 48).

**Topical chemotherapy**

In recent years, sole topical chemotherapy has proven to achieve complete tumor resolution and low recurrence rate with less injury (35, 64–66). This approach is preferred in diffuse and multifocal lesions, and no defined tumor margins. Topical chemotherapy allows treatment of the entire ocular surface and lower risk for limbal stem cell impairment. With topical treatment, however, the duration is longer and requires compliance of the patient. Furthermore, this treatment can be employed preoperatively as chemoreduction, and postoperatively, when margins are positive. However, caution should be paid as corneal melt, scleral melt, and cataract can occur if these agents are used with open conjunctival wounds or used excessively. Topical chemotherapy includes the use of interferon alpha 2b (IFNa-2b), 5-fluorouracil (5-FU) 1%, and mitomycin C (MMC). Their beneficial role involves immunomodulation, anti-proliferative, and anti-viral activity. All of these drugs require compounding. 5-FU has some advantages over MMC and IFNa-2b, as it is the most inexpensive, does not require refrigeration, and involves less frequent administration. MMC has more common and severe adverse effects than IFNa-2b or 5-FU, including corneal toxicity, limbal stem cell deficiency, and punctal stenosis. Side effects of topical 5-FU include pain and redness at the instillation site, eyelid swelling, conjunctival congestion, filamentary keratitis and, rarely, superficial stromal melting. Punctal or canalicular stenosis can occur with systemic 5-FU treatment, but not with topical 5-FU use. IFNa-2b is less toxic compared to both topical 5-FU and MMC. However, its use is often limited by cost and access to the drug. IFNa-2b can be used as topical or subconjunctival/perilesional formulation in the management of ocular surface tumors. When administered topically, IFNa-2b has the advantage of ease of use and minimal to no side effects, but it requires longer duration of treatment compared to 5-FU and MMC. Conversely, subconjunctival injections have more side effects than drops, including flu-like malaise that lasts for approximately 48 h, but have the benefits of faster resolution, better compliance, and no need for compounding. There is evidence on efficacy of topical chemotherapy for various premalignant and malignant lesions of the ocular surface, such as OSSN, diffuse and multifocal PAM with atypia, and recurrent conjunctival melanoma (16, 35, 36, 64–68).

**Ocular surface squamous neoplasia (OSSN)**

Topical 5-FU is generally used as first line agent in the primary treatment of preinvasive and invasive OSSN as well as an adjuvant after surgical excision. This drug is usually administered at a concentration of 1% in a cyclical pattern four times daily for one week followed by a drug holiday for three weeks. This monthly cycle is repeated on average of 4 to 6 cycles based on clinical response. Alternative regimens include administration of topical 5-FU 4 times daily for 2 days to 4 weeks, with variable weeks off (16, 65–68). Recently, subconjunctival/perilesional 5-FU injections for treatment of OSSN have shown to be effective and safe in the long term (69). IFNa-2b is a valid alternative to 5-FU for treatment of OSSN, however, it may have decreased efficacy compared to 5-FU in patients with underlying immunosuppression (65, 67, 68, 70). IFNa-2b for OSSN can be used as topical eye drops, subconjunctival/perilesional injections, or a combination of both. Topical and subconjunctival/perilesional IFNa-2b can be used as primary or adjuvant therapies. Treatment with topical IFNa-2b is generally administered at a dose of 1 million IU/mL four times a day continuously until one or two months after clinical resolution. The average time for clinical resolution is about 4 months. A dosage of topical 2-3 million IU/mL demonstrated similar efficacy. When used as a post-surgical adjuvant, topical IFNa-2b 1 million IU/mL is administered four times daily for a duration of 2 months post-operatively. IFNa-2b injected subconjunctival/perilesional is administered at a dose of 3 million IU/0.5 ml weekly until clinical resolution of OSSN, usually requiring 4 to 5 injections. The use of higher concentrations has also been reported, with
the highest being 10 million IU given once a month. There are evidences suggesting the use of intrale- sional injection of 3 million IU/0.5 ml or 10 million IU/ month IFN α-2b combined with 1 million IU topical IFN α-2b, as a primary modality for unresectable ex- tensive tumors. It also helps for reduction of tumor size prior to complete surgical excision (70).

MMC is generally considered as second line agent for OSSN. MMC can be used for primary treatment of OSSN, but can also be used as an adjuvant agent intraoperatively, and post-operatively in patients with positive conjunctival margins (65, 67, 68, 71, 72). When used as a primary therapy for OSSN, MMC is generally prescribed at a concentration between 0.02 and 0.04%. MMC is administered 4 times a day for 1 week followed by 2-3 weeks of no treatment. The length of the drug holiday depends on how long it takes the eye to recover from the 1 week of treatment. It usually takes a total of 3 cy- cles for the tumor to resolve. Alternative regimens include 7-14 day cycles. MMC can also be used intraoperatively during tumor excision, typically soaked on a sponge at a concentration of 0.02% and applied to the conjunctival margins for 1-3 min. Postoperatively, MMC can be used in patients with positive margins after the surface heals. The dose and protocol during post-operative use are similar to primary use (65, 67, 68). Topical chemotherapeutic agents for OSSN are listed in Table 3.

**Melanocytic epithelial tumors**

Topical chemotherapy is usually used as an adju- vant for conjunctival melanoma if surgical margins demonstrate PAM with atypia, but it can also be employed as a primary treatment in cases of dif- fuse or multifocal PAM with atypia and recurrent conjunctival melanoma. A commonly used dosing regimen for treatment of melanocytic lesions is two-week cycles of 0.04% MMC 4 times a day, followed by treatment discontinuation for 14 days (35, 36, 73). The use of topical IFNα-2b has been reported as a less toxic adjunctive therapy for mel- anocytic lesions, but evidence is limited (35, 74– 76). The use of 5-FU has not been investigated for ocular surface melanocytic neoplasms.

**Radiotherapy**

There are two forms of radiotherapy usually em- ployed for the treatment of ocular surface tumors, namely EBRT and plaque brachytherapy (44, 77). EBRT is a method for delivering high-energy x-rays to cancer cells while sparing surrounding tissues. It is

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>FORMULATION</th>
<th>DOSAGE</th>
<th>SIDE EFFECTS</th>
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<tbody>
<tr>
<td>5-FU</td>
<td>Topical: 1% drops Subconjunctival/perilesional Injections: 25 mg/mL at certain intervals.</td>
<td>4 times a day for 1 week and 3 weeks off. Mean 4-6 cycles (alternative: 4 times daily from 2 days to 4 weeks and variable weeks off).</td>
<td>Pain and redness at the instillation side, eyelid swelling, conjunctival congestion, filamentary keratitis and, rarely, superficial stromal melting.</td>
</tr>
<tr>
<td>IFN α-2b</td>
<td>Topical: 1 MIU/ml (Alternative: 2-3 MIU/ml). Subconjunctival injections: 3 MIU/0.5 ml (alternative: 10 MIU/month).</td>
<td>Topical: 4 times a day continuously until 1-2 months after resolution. Subconjunctival: 3 MIU/0.5 ml weekly injections until resolution (mean 4-5 weeks) or 10 MIU monthly. Topic post-surgical: 4 times a day continuously for 2 months.</td>
<td>Minimal side effects for drops, flu-like malaise with injection.</td>
</tr>
<tr>
<td>MMC</td>
<td>Topical: 0.02-0.04% drops</td>
<td>4 times a day for 1 week followed by 2-3 weeks off until the eye is quiet. Usually 3 cycles until resolution (Alternative: 7-14 day cycles).</td>
<td>Corneal toxicity, limbal stem cell deficiency, and punctal stenosis.</td>
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Table III. Topical chemotherapeutic agents for OSSN (16,65–72).
generally used to treat isolated conjunctival lymphoma and locally extensive, non-resectable tumors. Plaque brachytherapy, on the other hand, is provided with a device filled with radioactive seeds sutured to the ocular surface. Radiation sources include isotopes of iodine-125, palladium-103, strontium-90, and ruthenium-106. Unlike topical chemotherapy, plaque brachytherapy has the ability to treat deep in the sclera. This procedure is considered in patients with positive surgical margins and in those showing multiple recurrences, and it should be delayed until conjunctiva has healed (10, 21). More recently, radiotherapy techniques via surface applicator have been developed to avoid the use of an attached plaque (77). Side effects of radiotherapy include dry eye syndrome, punctate epithelial abnormalities and corneal ulceration, retinopathy, orbital fat tissue atrophy, and cataract development. In order to reduce radiation toxicity, a lower dose or smaller daily fractions can be used (77).

CONCLUSIONS
Tumors of the ocular surface include a broad clinical spectrum. The diagnosis of ocular surface tumors is primarily based on clinical evaluation and histological confirmation. Recently, new non-invasive diagnostic approaches including HR-OCT showed promise for use as adjuvant for histology. Treatment of ocular surface tumors is classically based on local excision with cryotherapy to the margins and/or radiotherapy. Topical chemotherapy recently demonstrated complete tumor resolution and a low recurrence rate with less injury if compared to surgical removal.

ETHICS

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Conflict of interests
The authors have declared no conflict of interests.

Availability of data and material
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Authors' contribution
Study conception and design: MS, FM, AL. Drafting of manuscript: FM, MS, AVC. Acquisition of images: MS, PS. Critical revision: MS, AL. All authors contributed to refinement of the study and approved the final manuscript. This manuscript has been read and approved by all the authors and each author believes that the manuscript represents honest work. All authors meet the requirements for authorship and all express full consent for publication on your esteemed Journal. All the authors contributed equally to conception, data collection, analysis and writing of this paper. Ethical approval: The study was realized in full compliance with the Declaration of Helsinki.

Consent to participate
Informed consent to publish personal or clinical details along with any identifying images was obtained from each patient.
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ORIGINAL ARTICLE

METRONOMIC CONTINUOUS ORAL CYCLOPHOSPHAMIDE (CPM) AS SECOND AND FURTHER LINE IN METASTATIC SOFT TISSUE SARCOMAS (STS) OF THE ADULT

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ABSTRACT

In metastatic soft tissue sarcomas (mSTS) second and further line of therapy are poorly defined. However many patients (pts), after first line therapy including Anthraclyclines progress in their disease and ask to be treated. Oral cyclophosphamide (CPM) was already used in breast cancer, prostate cancer and in one study in mSTS with contrasting results. Aim of our study was to define the feasibility, tolerability and activity of oral CPM as second and further line chemotherapy in mSTS with contrasting results. Aim of our study was to define the feasibility, tolerability and activity of oral CPM as second and further line chemotherapy in mSTS patients: 45 pts (19 M; 26 F) median age 60 (32-81), with pretreated mSTS were included. Oral CPM was given daily at total dose of 50 mg/day without interruption excepted for toxicity or progressive disease. Results: leiomyosarcoma 12, liposarcoma 10, MPNST 5, synovialsarcoma 4, indiffereniated sarcoma 4, other rarer subtypes 10. Sites of the primary tumor were: extremities 21, retroperitoneum 19, trunk 5.41 pts were metastatic, 4 locally relapsed. All 45 pts were pretreated with chemotherapy (17 were in II line, 18 in III line, 8 in IV line, 2 in V line). Median PS (ECOG) was 2. Median duration of therapy was 4.4 months (from 1 to 38 months). The 6-month PFS rate was 46%. Treatment was well tolerated: neutropenia grade 2 in 1 case, fatigue grade 2 in 7 patients, nausea grade 1-2 in 22 cases. No grade 3-4 side effects were recorded.
INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal malignancies diagnosed in approximately 2,500 patients in Italy each year (1) and with 5 years median survival of 53% (2). More than 70 histologic subtypes are recognized, many of them harboring molecular subtypes with specific biological behavior (3, 4). As localized disease STS can be cured in a multidisciplinary approach in 75% of the cases with surgical intervention + radio and chemotherapy (5). Unfortunately, STS metastasize mostly in the lung, and less frequently in liver and bone (6). When metastatic, the median survival is around 12 months and no effective therapy has been found until now (5). Standard Chemotherapy is based on anthracyclines ± Ifosfamide as first-line treatment but the PFS is about 4 months (5-7).

After failure of anthracyclines, second line therapy includes trabectedin in lipo and leiomyosarcoma (7), HD Ifosfamide in undifferentiated sarcoma, liposarcoma and synovial sarcoma (8), taxanes in angiosarcoma (9).

Third line therapy can be an option in good performance status patients, but the unique end point is palliation. Pazopanib as antiangiogenic agent has demonstrated some activity in this setting in non-adipocytic sarcoma (10), but few other drugs can be adopted: Eribulin in liposarcoma (11), Gemcitabine and Dacarbazine in leiomyosarcoma (12). Metronomic therapy can be an option. Metronomic chemotherapy (MC) is the regular administration of low-dose antitumoral drugs for a prolonged period of time with minimal or without drug-free intervals (12-15).

Oral CPM showed a mild activity and good tolerability in pretreated mSTS. It could be an appropriate solution as second and further line therapy and in unfit or elderly patients.

KEY WORDS

Metastatic soft tissue sarcomas; oral cyclophosphamide; metronomic therapy; chemotherapy; angiogenesis.

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This phase II monoinstitutional study evaluates the activity as second and further line of therapy of metronomic cyclophosphamide in metastatic soft tissue sarcomas. The results obtained showed a stabilization of the disease in most cases and a good profile of toxicity.

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Oral CPM showed a mild activity and good tolerability in pretreated mSTS. It could be an appropriate solution as second and further line therapy and in unfit or elderly patients.

KEY WORDS

Metastatic soft tissue sarcomas; oral cyclophosphamide; metronomic therapy; chemotherapy; angiogenesis.

IMPACT STATEMENT

This phase II monoinstitutional study evaluates the activity as second and further line of therapy of metronomic cyclophosphamide in metastatic soft tissue sarcomas. The results obtained showed a stabilization of the disease in most cases and a good profile of toxicity.

INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal malignancies diagnosed in approximately 2,500 patients in Italy each year (1) and with 5 years median survival of 53% (2). More than 70 histologic subtypes are recognized, many of them harboring molecular subtypes with specific biological behavior (3, 4). As localized disease STS can be cured in a multidisciplinary approach in 75% of the cases with surgical intervention + radio and chemotherapy (5). Unfortunately, STS metastasize mostly in the lung, and less frequently in liver and bone (6). When metastatic, the median survival is around 12 months and no effective therapy has been found until now (5). Standard Chemotherapy is based on anthracyclines ± Ifosfamide as first-line treatment but the PFS is about 4 months (5-7).

After failure of anthracyclines, second line therapy includes trabectedin in lipo and leiomyosarcoma (7), HD Ifosfamide in undifferentiated sarcoma, liposarcoma and synovial sarcoma (8), taxanes in angiosarcoma (9).

Third line therapy can be an option in good performance status patients, but the unique end point is palliation.

Pazopanib as antiangiogenic agent has demonstrated some activity in this setting in non-adipocytic sarcoma (10), but few other drugs can be adopted: Eribulin in liposarcoma (11), Gemcitabine and Dacarbazine in leiomyosarcoma (12). Metronomic therapy can be an option. Metronomic chemotherapy (MC) is the regular administration of low-dose antitumoral drugs for a prolonged period of time with minimal or without drug-free intervals (12-15).

Oral CPM showed a mild activity and good tolerability in pretreated mSTS. It could be an appropriate solution as second and further line therapy and in unfit or elderly patients.
The best response to treatment was evaluated according to RECIST criteria (24). Progression-free survival (PFS) was defined as the time from the start of metronomic chemotherapy until disease progression, death or last patient contact. Overall survival (OS) was defined as the time from the start of metronomic chemotherapy until death or last patient contact. Toxicity was classified according with NCI criteria (25).

**Statistical analysis**
The statistical analysis of demographics and clinical outcome is based on all data available up to the cutoff date of December 2018. Survival rates were estimated with the use of the Kaplan–Meier method.

### RESULTS
Baseline characteristics of the 45 patients, are summarized in **table I**. Metronomic therapy consisted in CPM 50 mg/day as continuous oral administration. A blood cell count was performed every fifteen days. If neutrophils were below 1000/mm³ or platelets < 100,000/mm³, respectively, treatment was delayed until recovery. Oral Metoclopramide or Ondansetron were admitted in case of nausea and vomiting. The treatment was continued until disease progression, unacceptable toxicity or refusal of the Patient.

<table>
<thead>
<tr>
<th><strong>POPULATION’S CHARACTERISTICS</strong></th>
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<td>Metacronous</td>
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<table>
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<tr>
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<td>Liposarcoma</td>
<td>10</td>
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<tr>
<td>MPNST</td>
<td>5</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Undifferentiated sarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Other histotypes</td>
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<table>
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<tr>
<td>1</td>
<td>2</td>
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<tr>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
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<table>
<thead>
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<th><strong>LINE OF THERAPY</strong></th>
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<tbody>
<tr>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Metronomic regime CPM 50 mg/die</td>
<td>45</td>
</tr>
</tbody>
</table>

**Table I. Patients characteristics and patterns of treatment.**

As presented in **table II** the median exposition to metronomic therapy was 4.4 months ranging from 1 to 38 months. The median PFS was 4.0 months [95% CI: 2.6-9.8]. The 6-month PFS rate was 46%.

At the time of analysis, all 45 patients had died. All deaths were the result of progression of sarcoma. The median OS was 10.2 months [95% CI: 6.4 -13.2]. The 6-month OS rate was 64% and 32% at one year.

were pretreated with at least one line of chemotherapy. The study was approved by the local ethical committee. The patients characteristics are resumed in **table I**. Metronomic therapy consisted in CPM 50 mg/day as continuous oral administration. A blood cell count was performed every fifteen days.

If neutrophils were below 1000/mm³ or platelets < 100,000/mm³, respectively, treatment was delayed until recovery. Oral Metoclopramide or Ondansetron were admitted in case of nausea and vomiting. The treatment was continued until disease progression, unacceptable toxicity or refusal of the Patient.
Cyclophosphamide (CPM) is the most widely explored agent in metronomic approach since either in vitro studies or in clinical experience have demonstrated a long term antiangiogenetic effect with a lethal activity to endothelial cells (15, 16, 28-30). Breast cancer (19, 31, 32), prostate cancer (18, 33, 34) are the two tumors with more studies on metronomic therapy. Soft tissue sarcomas are rare tumors, with more than seventy different histological types (3). Metastatic disease can be treated with chemotherapy with dismal results: 4-5 months PFS and 12 months Median Overall Survival (5, 6, 35). One single institution experience with CPM 100 mg/day for 21 days every 28 days as second and further line of therapy in elderly or mild performance status patients suggests that Metronomic therapy may represent a choice in palliative setting (21). Elderly and low performance status patients are often excluded from clinical studies and no specific option of therapy is available. In our study we did not record complete or partial responses, but stable disease was seen in 48% of the patients. Median PFS of 4.0 months is superimposable to that of more toxic agents used in second line therapy (5-8, 10-12, 35). In Mir and coll. study (22) the elderly STS patients were treated with CPM+ prednisone either as first or second line chemotherapy. This French group had one complete and 6 partial response (ORR 26.6%) and 11 stable disease. The median PFS was 6, 8 months and 1 year survival was 65.4%. Italiano and coll. used in a younger population (49 years as median age) etoposide with metronomic schedule (100 mg/day for 21 consecutive day every 4 weeks) as second line therapy after doxorubicin containing therapy (21). The author recorded one partial response, 42% stable disease and 1-year overall survival of 31%. All the other experiences in STS with metronomic CPM are reported in pediatric patients, but age-related histology vary. Embryonal rhabdomyosarcoma occurs almost exclusively in children and the percentage of response rate and survival are higher than in adults types of mSTS (36-41).

In animal model Ma and coll. introduced a multidosing metronomic therapy combining axitinib a TKI antiangiogenic drug + cyclophosphamide. The combination showed a good activity both in vitro and in animal model and should be proposed.

### DISCUSSION

Metronomic therapy opens a shift in the treatment of cancer.

In 1980's and 1990's an increasing dosing approach was dominant with escalating dose density and dose intensity made possible by blood stem cell support and a better knowledge of supportive care (14, 26).

The results of dose escalation lead to some results in lymphomas, myelomas, leukemia but not in solid tumors (14).

No results at all in STS (5, 6).

At the beginning of the new millennium, the concept of “cancer as chronic disease” started a different paradigm for dosing chemotherapy (1, 14). Metronomic therapy is based on the concept to target neoangiogenesis, immunology and intracellular pathways of cancer cells, leading to a control on the growth, replication, neovascularization, and over the ability to metastasize of neoplastic cells (13-16). The aims of the two therapies are clearly different:

- high dose therapy targets the replicating cells and kills them following the Skipper and Schabel rules (14, 27);
- metronomic therapy, on the contrary, determines the growth control, restores the apoptotic process and hampers the neoangiogenesis of the tumor slowing the metastatic diffusion (13-16).

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### EFFICACY OUTCOMES

<table>
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<th>Complete response</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>22</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>23</td>
</tr>
<tr>
<td>PFS median</td>
<td>4.0 months</td>
</tr>
<tr>
<td>6 months survival rate</td>
<td>64%</td>
</tr>
<tr>
<td>12 months survival rate</td>
<td>32%</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>10.2 months</td>
</tr>
</tbody>
</table>

**Table II.** Results.

No complete or partial responses were seen. Twenty two stable disease (48%) for a median PFS of 3.8 months were recorded.

### TOXICITY

<table>
<thead>
<tr>
<th>Neutropenia (G 2)</th>
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</thead>
<tbody>
<tr>
<td>Fatigue (G 2)</td>
<td>7</td>
</tr>
<tr>
<td>Nausea and Vomiting (G 2)</td>
<td>22</td>
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</tbody>
</table>

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for future clinical trials (42). However, some experiences as case report were published with pazopanib, another TKI anti-VEGFR approved in metastatic STS at the dose of 800 mg/day (10). Groenland and coll. reported two cases of patients with mSTS treated with pazopanib 200 mg/day personalized dose after grade 4 hematologic toxicity with standard dose. The serum active concentration of pazopanib was > 20,5 mg/L and demonstrated a relevant effect on the disease (43). CPM metronomic regime was developed to optimize the antitumor activity as well as to reduce toxicity (13-16, 21, 22). As matter of fact in our study a low hematological and gastrointestinal side effects were recorded. The same results were reported by Mir and coll. (22); whether in the study of Italiano and coll with metronomic etoposide published 4% grade 4 neutropenia (21). Limitation of our study are the heterogeneous population involved, with different age, performance status, dissimilar histology subtypes of STS and various lines of previous therapy. As most studies investigating metronomic therapy in different tumors, our study is a single institution, non-randomized phase II trial. Furthermore, in STS we recognize slow growing tumors with low proliferating cell population in contrast with highly aggressive tumors as angiosarcoma rapidly proliferating (3, 6). The stabilization of disease in some cases could be the consequence of the biological characteristics of the disease, rather than the effect of metronomic cyclophosphamide. In conclusion metronomic therapy could be considered a choice as second and further line therapy in mSTS. Some aspects support metronomic therapy in specific clinical situations: - stabilization of the disease for a variable period of time in heavily pretreated patients; - low degree of toxicity; - good compliance from the patients; - possible synergistic effect with biological antiangiogenic therapy; - low cost therapy.

On the contrary, some points need more investigations: - the efficacious daily dose of metronomic CPM: 50 mg or 100 mg daily? - continuous or interrupted treatment? (3 weeks in, 1 week out);

- CPM as single agent or combined with other drugs? (as vinorelbine or methotrexate in breast cancer); - identification of biomarkers to predict the activity of the drug as antiangiogenic; - the precise identification of the population who could benefit from metronomic therapy.

To face these problems the Italian Sarcoma cooperative Group (ISG) has designed a protocol comparing metronomic cyclophosphamide versus doxorubicin as first line treatment in elderly patients with mSTS. The end points are PFS, OS, ORR, toxicity and quality of life. The ISG study is ongoing and the results could be useful to answer some of the open questions about metronomic therapy in mSTS in the specific population of the elderly patients. In younger population and in specific subtypes of STS more specific studies are requested.

ETHICS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The authors have declared no conflict of interests.

Availability of data and material

The data underlying this article are stored by the Data Manager Dr G. Cuomo. at Ospedale San Giovanni Bosco (Turin, Italy) and can be shared just before a reasonable request to the corresponding author.

Authors’ contribution

All the authors contributed equally to conception, data collection and discussion of this paper. CO: statistical analysis; AB and AC: writing.

Ethical approval

The study was approved by the Ethics Committee of the Humanitas Hospital of Gradenigo (Turin, Italy).

Consent to participate

Informed consent is attached to medical records.
REFERENCES


COVID-19 OUTBREAK IN ITALY. REPORT OF 20 CANCER PATIENTS WITH COVID-19 TREATED AT HOME DURING THE FIRST WAVE

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ABSTRACT
The published studies of patients with COVID-19 and cancer are done on hospitalized patients, and data on early outpatient treatment of symptomatic COVID-19 cancer patients are unavailable in English literature. This study included a retrospective, single-center case series of 20 consecutive symptomatic non-hospitalized adults with laboratory confirmed or probable COVID-19 infection. The diagnosis of pneumonia was done with portable ultrasound (US). The treatment was based on hydroxychloroquine (HCQ) plus azithromycin (AZ), drugs allowed during the first wave. Oxygen was delivered when necessary, and enoxaparine was done in bedridden patients. The primary endpoint was clinical improvement or hospitalization considered as worsening of clinical conditions. The secondary endpoints were mortality at day 30 and at day 60. A finger oximeter was delivered to each patient and all patients were monitored by tele-medicine, the side effects of treatment were registered and reported. From March 13rd to May 26th, 2020, 180 patients with laboratory - confirmed COVID-19 infection or with epidemiologically linked exposure to a person with laboratory - confirmed infection were managed at home for COVID-19 in the district of Piacenza, Emilia Romagna Region. Among these 180 patients, 20 (11.11%) had cancer and form the basis of this report. There were 13 females (65%) and 7 males (35%), the majority of cancers were breast (40%) and gastrointestinal (30%). Seven patients (35%) were on active anticancer treatment when infected and all with metastatic disease, 13 patients (65%)
were off therapy. Only one patient was hospitalized (5%) and no patients died at 30 and 60 days. All 20 patients overcame the infection. The early home management of COVID-19 cancer patients allowed a very low hospitalization rate and no deaths were registered in this series. We believe that COVID-19 cancer patients should be treated precociously at home and monitored by telemedicine. 

**KEY WORDS**
SARS-COV-2; cancer; outpatients; COVID-19; telemedicine; hospitalization rate.

**INTRODUCTION**
A novel coronavirus named coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, in December 2019, and it has quickly spread globally (1). Cancer patients might be at higher risk of acquiring infection because poor general conditions, systemic immunosuppressive state caused by cancer itself and/or anticancer treatment such as chemotherapy, radiation, surgery, steroids, etc. In addition cancer patients have frequent scheduled visits to hospitals and clinics that can increase the risk to catch COVID-19 (2). The district of Piacenza, Emilia Romagna Region, is very near to the epicenter of the outbreak of COVID-19 in Italy (10 minutes by car), where on February 21st there was the first Italian case, and the catastrophic nature of North Italy outbreak has been widely publicized (3, 4). The National Health Commission published guidelines that classified SARS-CoV-2 infections in 4 groups (mild type, moderate type, severe type and critical type) (5, 6). During the first pandemic wave, hydroxychloroquine (HCQ) with or without antiviral treatment has been initially incorporated in our national guidelines to treat COVID-19 (7, 8), and it was available until May 26th, 2020. In the district of Piacenza, a week later the 21st February 2020, the Emergency Department of the Piacenza hospital was overcrowded with COVID-19 infected people already in serious conditions. All these patients had a story of days or weeks spent at their home with fever, cough, fatigue, exertional dyspnea at first, then dyspnea at rest, that finally required the urgent hospitalization. All these patients were treated at home only with antipyretics like paracetamol, several with large spectrum antibiotics, like amoxicillin, and not any with HCQ or with antiretroviral or azithromycin (AZ). Since the treatment of patients who were admitted to the Piacenza hospital, was based on HCQ tablets 400 mg daily plus darunavir and cobicistat (DC) 800/150 daily for 7 days (8), we decided to perform strategic interventions to treat early at home COVID-19 infected cancer patients at the onset of symptoms avoiding to rest at home without medical care and avoiding the rapid progressive worsening of the patients. In this study, we did a comprehensive retrospective evaluation of cancer patients with COVID-19 infection, mild, moderate and severe type, precociously treated at home, in the district of Piacenza and neighboring areas from March 13 to May 26th, 2020.

**MATERIALS AND METHODS**
At the end of February 2020, the district of Piacenza (North Italy), a taskforce program finalized to diagnosis, treatment, check and monitoring of patients affected by COVID-19, was constituted with units, formed by a medical doctor and a nurse equipped with personal protective equipment (PPE), medical car, portable ultrasound (US), portable electrocardiography finger oximeters, kits for nasopharyngeal swab and for blood samples, kits of drugs with: DC 800/150 mg, HCQ tablets 200 mg, steroids, prednisone 25 mg, enoxaparin subcutaneously 4,000 or 6,000 Unit and AZ tablets 500 mg. Patients with suspected symptoms of COVID-19 infection such as fever, cough, dyspnea can directly call the task force or call their family doctor, that activate the task force and the patients are promptly visited at their home. This program was called “The Piacenza Model”. The COVID-19 severity was classified as

**IMPACT STATEMENT**
Although a small patient cohort was analyzed, our experience showed that the early diagnosis and treatment of COVID-19 infection in cancer patients could avoid hospitalization and death, prompting the implementation of early home management and monitoring through telemedicine.
follows in accordance with the diagnosis and treatment of COVID-19 guidelines (5): mild type: the clinical symptoms are mild with no abnormal radiological findings; moderate type: fever, cough and other symptoms are presented with pneumonia on chest computed tomography or sonography; severe type: disease is classified as if one of the following conditions is met: respiratory distress, respiratory rate ≥ 30 per men; oxygen saturation on room air at rest ≤ 93%; partial pressure of oxygen in arterial blood / fraction of inspired oxygen ≤ 300 mmHg. Critical Type: one of the following conditions has to be met: respiratory failure occurs and mechanical ventilation is required; shock occurs; patients with other organ dysfunction need intensive care unit monitoring treatment. Chest ultrasound is performed as previously reported by an expert physician (9, 10) and nasopharyngeal swab specimens are collected according to the Center for Disease Central and Prevention Guidelines and performed with reverse transcription polymerase chain reaction (RT-PCR) (11). For patients without a recent electrocardiogram (ECG) and whit history of heart disease, ECG was carried out to allow HCQ therapy. The diagnosis of COVID-19 was based on typical symptoms, lung involvement on chest ultrasonography, and confirmed by RT-PCR for SARS-COV-2 detection in the majority of patients. However, in patients without RT-PCR for SARS-COV-2 detection, the diagnosis of COVID-19 was based on compatible symptoms after a high risk exposure. Patients with mild type of COVID-19 infection and without risk factors were treated only with symptomatic drugs like paracetamol; treatment with HCQ was reserved to patients with mild type presenting at least one of these risk factors: age ≥ 60 years, obesity, hypertension, diabetes, cancer, Chronic Obstructive Pulmonary Disease (COPD), chronic ischemic heart disease. For patients with COVID-19 pneumonia causing respiratory illness, the treatment is immediately started with HCQ 400 mg twice daily on day one followed by 200 mg twice daily alone for six days or HCQ plus AZ 500/daily for 6 days. A finger oximeter was delivered to each patient and every day the value of oxygen saturation and clinic symptoms are communicated by the patient on a phone or tablet to the task force’s nurse and registered three times/day. When oxygen saturation SaO2 is of 93 or less, oxygen therapy is delivered at home. For bedridden patients, enoxaparine 4.000 to 6.000 UI/daily subcutaneously is done, and when body temperature is above 38 °C, paracetamol 500 mg is recommended. Prednisone 35.5 mg daily was added to patients with severe dyspnea. Treatment was offered to male and no pregnant female patients, 18 years or older. The treatment with HCQ was not performed in patients with QTc prolonged or with a story of favism. In this study, we report data of oncologic patients with laboratory-confirmed COVID-19 infection.

**Patient monitoring**

Patients were monitored on a phone or tablet by doctors or trained nurses. Three times per day for the evaluation of these parameters: finger oximeter, fever, cough, dyspnea, fatigue, other symptoms, ability to eat, to take drugs. Adverse effects of drugs were monitored. Patients with moderate or severe COVID-19 type were revisited every three days until they recovered. Hospitalization was evaluated for patients with progressive dyspnea.

**Patient outcome measuring**

The primary endpoint of this program was clinical improvement or hospitalization. Secondary endpoint was mortality at day 30 and at day 60. Discontinuation of oncologic treatment was registered; adverse events related to the treatment were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version N. 5 and reported (12).

**Statistical analysis**

Patients were registered with a unique recognition code, for everyone we recorded in a Microsoft Excel file (Microsoft Office version 2010): age, sex, symptoms and date of onset, comorbidities, COVID-19 therapy, COVID-19 severity, oxygen therapy, hospitalization and outcome. Quantitative variables are described by mean ± standard deviation; qualitative variables are described by absolute and percentage frequencies. Comparisons of covariates were conducted using chi2 or Fisher’s exact test for categorical variables and t-test or Mann Whitney test for continuous variables. All analyses were performed using STATA version 16 statistical software, with 2-sided significance tests and the 5% significance level. This retrospective study was approved by the Local Ethics Committee (Institutional review board IRB (approval number 494/2020/OSS/AUSLPC) ASL of Piacenza. The informed consent was obtained from each patient. In this retrospective study, we analyzed the data of 20 consecutive cancer patients affected by SARS-COV-2 diagnosed and treated at home.
## RESULTS

From March 13 to May 26th, 2020 180 patients with laboratory-confirmed COVID-19 infection were visited and treated at home, 72 men and 108 women, the mean age was 58.10±15.63 years (range 18-91), 97 (53.88%) patients showed one or more comorbidities, 20 (11.11%) had cancer. We report here the results of 20 consecutive cancer patients with COVID-19. Clinical and demographic characteristics are reported in Table I. There were 13 females (65%) and 7 males (35%), the majority of cancers were breast (40%) and gastrointestinal (30%), the other patients had lung (5%), prostate(5%), endometrium (10%) and neuroendocrine cancer (10%). Seven patients (35%), all with metastatic disease, were on active anticancer treatment.

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>PATIENTS (TOTAL = 20)</th>
<th>SEVERITY OF COVID-19</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MILD (N = 7)</td>
<td>MODERATE (N = 10)</td>
</tr>
<tr>
<td>Age mean ± ds, range</td>
<td>61.85 ± 12.27 (32-83)</td>
<td>63.14 ± 13.61 (46-83)</td>
<td>59.3 ± 13.13 (32-75)</td>
</tr>
<tr>
<td>GENDER</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male n (%)</td>
<td>7 (35)</td>
<td>4 (57.14)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>13 (65)</td>
<td>3 (42.85)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>COMORBIDITIES N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (20)</td>
<td>1 (14.29)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease n (%)</td>
<td>4 (20)</td>
<td>2 (28.57)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>4 (20)</td>
<td>2 (28.57)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Coronary disease n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other n (%)</td>
<td>4 (20)</td>
<td>2 (28.57)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>TUMOR SITE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>8 (40)</td>
<td>2 (28.57)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6 (30)</td>
<td>1 (14.29)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (30)</td>
<td>4 (57.14)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>ACTIVE CANCER TREATMENT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (35)</td>
<td>3 (42.86)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>No</td>
<td>13 (65)</td>
<td>4 (57.14)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>SYMPTOMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever n (%)</td>
<td>19 (95)</td>
<td>7 (100)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Cough n (%)</td>
<td>13 (65)</td>
<td>3 (42.86)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Dyspnea n (%)</td>
<td>5 (25)</td>
<td>0 (0)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Diarrhea n (%)</td>
<td>5 (25)</td>
<td>2 (28.57)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Fatigue n (%)</td>
<td>3 (15)</td>
<td>1 (14.29)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Dysgeusia n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other n (%)</td>
<td>5 (25)</td>
<td>4 (57.14)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Duration of symptoms before treatment (days) mean ± ds, range</td>
<td>6.35 ± 2.81 (3-12)</td>
<td>6.14 ± 2.80 (3-10)</td>
<td>5.9 ± 3.07 (3-12)</td>
</tr>
<tr>
<td>Treatment for COVID-19 (HCQ + AZ)</td>
<td>19 (95)</td>
<td>6 (85.71)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>OUTCOME</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead at 30 days</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dead at 60 days</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hospitalized n (%)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table I. Clinical and demographic characteristics of oncologic COVID-19 patients diagnosed and treated at home based on severity of COVID-19. AZ: azithromycin; HCQ: hydroxychloroquine.
treatment (2 chemotherapy, 2 immunotherapy and 3 hormone therapy), while 13 patients (65%) were not. The most frequent symptoms were fever (95%) and cough (65%). 7 (35%) patients showed mild, 10 (50%) moderate and 3 (15%) severe COVID-19 type (5). The most frequent comorbidities were hypertension (20%), diabetes (20%) and chronic obstructive pulmonary disease (20%). The duration of symptoms before treatment was higher in patients with severe COVID-19 (8.33 ± 1.53 days) when compared to patients with moderate (5.9 ± 3.07 days) and mild type (6.14 ± 2.80 days). 19 patients were treated with low-dose HCQ (800 mg day 1, subsequently 400 mg daily for 6 additional days), plus AZ (500 mg daily for 6 days). 1 patient with mild COVID-19 type was treated with non-steroid anti-inflammatory drugs. Primary endpoint: only 1 patient (5%), with stage III pancreatic cancer, not on active treatment, was hospitalized and was discharged after 3 days; secondary endpoint: no patients died at 30 and 60 days. The treatment with HCQ and AZ was well tolerated in the 19 cancer patients, only 1 patient (5.26%) had diarrhea and 1 (5.26%) headache and abdominal pain.

DISCUSSION

In this report, we describe the first series of cancer patients with COVID-19 treated early at home in a western country. Italy has been the first country in Europe experiencing an outbreak of COVID-19 and Piacenza is very near to the epicenter of Lombardy's outbreak. Oncology scientific societies have quickly released guidelines on cancer care during the pandemic, suggesting to use telemedicine to reduce the spread of infection (13-15). We are aware that our results provide some descriptive information, but the prognostic role of these findings is still potential and should be clarified by further and large-scale studies. These 20 cancer patients with COVID-19 infection manifested respiratory symptoms including fever, cough and shortness of breath. In our study, there were 3 severely ill patients, 10 moderate and 7 mild patients. However, we observed that the disease of most patients showed a moderate course. In particular, only 1 (5%) of those 20 patients was hospitalized for progressive dyspnea and discharged after 3 days. We previously reported 25 cancer patients with COVID-19 treated in our hospital: nine (36%) of these patients died, while 16 (64%) overcame the infection (8). In a second report (16), a retrospective study was performed in the hospitals of our district, including 51 hospitalized cancer patients with COVID-19, 25 of these 51 patients (49%) died, 12 of 51 (23.53%) owing to cancer and 13 of 51 (25.49%) owing to COVID-19. In our opinion, with the limits of retrospective studies and with different settings of cancer patients with COVID-19 (likely more serious and advanced disease in hospitalized patients), the early COVID-19 treatment allowed a more favorable outcome. It must be emphasized that COVID-19 hospitalized patients, above all, when critically ill, may be associated with hospital-acquired infections (HAIs). A recent study showed that 46% of 774 COVID-19 hospitalized patients developed 759 HAIDs and 234 patients (30%) died in ICU (17). These data support the strategy to treat early at home (when possible) cancer patients with COVID-19 avoiding hospitalization and death. The integration between early treatment and home management of COVID-19 patients could be an element of success in the management of the emergency. However, further assessments are required on the effectiveness and impact of the adopted model.

CONCLUSIONS

Although a small patient cohort was analyzed, our experience showed that the early diagnosis and treatment of COVID-19 infection in cancer patients could avoid hospitalization and death, prompting the implementation of early home management and monitoring through telemedicine.

ETHICS

Fundings
There were no institutional or private fundings for this article.

Conflict of interests
The authors have declared no conflict of interests.

Availability of data and material
The data underlying this article can be shared just before a reasonable request to the corresponding author.

Authors' contribution
All the authors contributed equally to conception, data collection, analysis and writing of this paper.
REFERENCES


CASE REPORT

PULMONARY CAPILLARY HEMANGIOMATOSIS INDUCED BY SARS-COV-2 INFECTION. A CASE REPORT

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ABSTRACT

Human morbidity and mortality associated with the infection SARS-CoV-2 is mainly due to pneumonia. The histological pattern of lungs is characterized by diffuse alveolar damage (DAD) and hyaline membranes. Vascular changes, including endothelial disfunction in the alveolar septal capillaries followed by thrombosis and disseminated intravascular coagulation, are frequently associated. Recently, further microvascular changes leading to new blood vessel growth through intussusceptive angiogenesis and distortion of microvascular architecture have been reported in lungs from patients...
died because of COVID-19. Here we report a case of COVID-19 in a 63-year-old patient affected by progressive respiratory failure. At histology, DAD was associated with distinctive vascular changes, including alveolar capillary microthrombi and thrombosis of arterial vessels. Moreover, a marked proliferation of small capillaries extending from the alveolar septa and compressing the adjacent alveoli was observed, allowing the diagnosis of pulmonary capillary hemangiomatosis (PCH). This report of PCH in a patient affected by COVID-19 reinforces the hypothesis of the major role played by endothelial dysfunction, capillary thrombosis and neoangiogenesis in SARS-CoV-2 infection and suggests that new blood vessel growth may evolve toward PCH, ending to the disruption of lung architecture.

**KEY WORDS**
Pulmonary capillary angiomatosis; COVID-19; SARS-CoV2.

**INTRODUCTION**
Human morbidity and mortality associated with infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is mainly due to progressive life-threatening pneumonia (1, 2). At imaging assessment, computed tomography (CT) imaging evidences peripheral ground-glass opacities indicative for the diagnosis of acute respiratory distress syndrome (ARDS) (3). The histological pattern of lungs, at autopsy, is characterized by necrosis of alveolar lining cells (type I pneumocytes), hyaline membranes, alveolar and interstitial edema and hemorrhages, i.e. the typical features of diffuse alveolar damage (DAD) (4, 5). However, lung pathology in COVID-19 patients is not restricted to alveolar damage: vascular changes are frequently associated with severe SARS-CoV-2 infection. Pulmonary thrombosis and disseminated intravascular coagulation, evidenced at histology by the formation of fibrin thrombi in the alveolar septa capillaries, are frequently detected in COVID-19 lung disease (6, 7). Recently, microvascular changes have been described in lungs from patients died from COVID-19, leading to new blood vessel formation, ending with distortion of the microvascular architecture of the lungs (8). By the use of scanning electron microscopy (SEM), structurally deformed capillaries were found in COVID-19 lungs, whereas transmission electron microscopy (TEM) revealed severe changes in endothelial cells in lungs from patients died from ARDS secondary to SARS-CoV-2 infection (9).

All these data taken together, vascular changes, including endothelial injury, widespread thrombosis of alveolar capillaries and new vessel growth, have been proposed as distinctive features of DAD due to SARS-CoV-2 infection, being absent in DAD associated with other etiologies (8). A recent proteomic analysis of 144 autopsies in COVID-19 patients evidenced dysregulation in multiple organs of key factors involved in angiogenesis, with 139 angiogenesis-related proteins significantly dysregulated that characterize a multi-organ proteomic landscape typical of COVID-19 (10).

Here we report a case of diffuse alveolar damage in a patient died with COVID-19, associated with a marked capillary proliferation leading to a pattern of pulmonary capillary hemangiomatosis (PCH).

**Case report**
A male patient, aged 63 years, developed a progressive respiratory failure. The patient died at home before medical intervention. Post-mortem molecular tests, performed by nasopharyngeal swabs, revealed SARS-CoV-2 infection. At autopsy, lungs were heavy (right lung 1,100 g; left lung 920 g), reddish in colour, diffusely edematous and showed a firm consistency. Microscopic examination of the lungs evidenced diffuse alveolar damage in the acute stage. Hyaline membranes were associated with marked congestion of larger veins and septal capillaries, alveolar and interstitial edema, fibro-hemorrhagic alveolitis and focal type II pneumocyte hyperplasia (figure 1). Lymphocyte and monocyte infiltrations

**IMPACT STATEMENT**
Endothelial dysfunction, capillary thrombosis and neoangiogenesis with new blood vessel growth induced by SARS-CoV-2 may evolve toward pulmonary capillary hemangiomatosis and lung architecture disruption.
were mild and patchy. In multiple lung specimens, distinctive vascular changes were also detected, consisting in alveolar capillary microthrombi and thrombosis of arterial vessels (Figure 2). Moreover, in some lung specimens we observed a marked proliferation of small capillaries, extending from the

Figure 1. Diffuse alveolar damage. Hyaline membranes, hemorrhagic alveolitis, congestion of septa capillaries, type II pneumocyte hyperplasia.

Figure 2. Thrombosis of an arterial vessel surrounded by marked capillary proliferation and alveolar collapse.

Figure 3. Marked proliferation of capillary vessels, extending from the inter-alveolar septa into the surrounding alveolar and vascular structures.

Figure 4. a. Residual alveoli surrounded and infiltrated by proliferating capillaries at low power. b. At high power.
alveolar septa and compressing the adjacent alveolar structures (figure 3). The lumen of the proliferating capillaries was occupied by microthrombi. The disordered capillary proliferation irregularly spread, involving pre-existing pulmonary vessels and adjacent airways (figures 4 a, b). At immunohistochemistry, proliferating vascular structures showed strong and diffuse immunostaining for CD31, CD34 and focal immunoreactivity for WT1.

DISCUSSION
The complexity of pathological changes observed in the lungs of patients affected by COVID-19 has been recently underlined by multiple reports on the different molecular pathways triggered by SARS-CoV-2 (11). Among them, vascular changes of lung vasculature, including endothelial cell dysfunction, endothelialitis (12), thrombosis of septal capillaries (13) and thrombosis of pulmonary arteries (14) have been proposed as distinguishing elementary lesions of COVID-19 from ARDS due to influenza infection (14). Moreover, previous papers evidenced the occurrence, in lungs from patients infected by SARS-CoV-2, of new vessel growth through a mechanism of intussusceptive angiogenesis (14). Neoangiogenesis was hypothesized to be the consequence of tissue hypoxia, caused by the high degree of endothelial damage and capillary thrombosis due to SARS-CoV-2 infection. In the case reported here, the hypothesis that pulmonary vessels represent one of the main targets for COVID-19 is confirmed by the detection of widespread lesions of endothelium, associated with diffuse intravascular coagulation in all the segments of lung vasculature. Moreover, our findings lay stress on the ability of SARS-CoV-2 to trigger a previously unreported proliferation of lung capillaries. In this case of lung disease due to COVID-19, proliferating vascular structures extended from the alveolar septa, infiltrating the structures of the pulmonary parenchyma, including alveoli, veins, and interstitial structures. These findings were at the basis of the diagnosis of pulmonary capillary hemangiomatosis (PCH), a rare and controversial entity often associated with pulmonary hypertension (15, 16). The underlying pathogenetic mechanisms of PCH are poorly understood. Recently, intussusceptive angiogenesis, a process of dividing pre-existing capillaries by formation of intravascular pillars, has been hypothesized to be involved in the pathogenesis of PCH (17). According to this hypothesis, venous and capillary occlusion, caused by a widespread thrombosis favoured by SARS-CoV-2 infection, might increase stretching forces in pulmonary capillaries, inducing intussusceptive neoangiogenesis, ending with the insurgence of PCH in COVID-19 pneumonia.

In conclusion, our report of PCH in a patient affected by COVID-19 reinforces previous reports on the major role played by endothelial dysfunction (18), endothelialitis, thrombosis (8) and neo-angiogenesis (14) in lung disease due to SARS-CoV-2 infection, and suggests that SARS-CoV-2 induced neoangiogenesis may evolve toward capillary hemangiomatosis, ending with disruption of the lung architecture, a typical feature of PCH.

ETHICS
Fundings
There were no institutional or private fundings for this article.

Conflict of interests
The authors have declared no conflict of interests.

Availability of data and material
All the data supporting the findings of this study are available within the article and can be shared just before a reasonable request to the corresponding author.

Authors’ contribution
All the authors contributed equally to conception, data collection, analysis and writing of this paper.

Ethical approval
Studies have been performed according to the Declaration of Helsinki (World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-4. Doi: 10.1001/jama.2013.281053). The procedures have been approved by a local ethics committee (date: 27/02/2021; approval number/code: PG/2021/1531; name of the ethics approving committee: Comitato Etico Indipendente Azienda Ospedaliero Universitaria di Cagliari).

Consent to participate
Informed, written consent has not been obtained because the patient was dead.
REFERENCES

INTERVIEW TO PROF. MASSIMO DI MAIO

IMPLEMENTING CLINICAL TRIALS IN ONCOLOGY
WITH QUALITY OF LIFE ASSESSMENT AND PATIENT
REPORTED OUTCOMES. AN INTERVIEW TO EXPLORE
THE ROAD TOWARDS A MORE PATIENT-CENTERED
APPROACH

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Health-related quality of life (QoL) is universally considered a measure of clinical benefit for patients with cancer, but its inclusion in clinical trials has historically been suboptimal. The recognition of the role of QoL and patient-reported outcomes in the evaluation of new agents by regulatory agencies and in the definition of treatment value is constantly increasing. ARO editors asked Prof. Massimo Di Maio, from the Department of Oncology, University of Turin and National Secretary of the Italian Association of Medical Oncology, critical questions about the use of patient-reported outcomes in clinical trials conducted in Oncology.

Massimo Di Maio is associate Professor of Medical Oncology at Department of Oncology, University of Turin, Italy, since 2014, and director of Medical Oncology at Mauriziano Hospital, Turin, since 2016. In 1999, he obtained degree cum laude in Medicine and Surgery at the Federico II University of Naples, Italy. In 2003, he graduated from the Specialty School in Oncology at the same University. From 2000 to 2006 and from 2008 to 2014 he worked at the Clinical Trials Unit of the National Cancer Institute G. Pascale Foundation, in Naples, Italy, where he was involved in the planning, conducting and analysis of clinical trials. His main areas of interest are the methodology of clinical trials and meta-analyses in Oncology and the use of patient-reported outcomes in clinical research and in clinical practice. Prof. Di Maio has been invited as speaker at many national and international meetings and has authored more than 300 publications in international peer-reviewed journals (H-Index April 2021: 45 according to Scopus). Additionally, Prof. Di Maio is an active member of the Associazione Italiana di Oncologia Medica (Italian Association of Medical Oncology, AIOM) and the European Society of Medical Oncology (ESMO). Between 2009 and 2013, Prof. Di Maio acted as national coordinator of the AIOM Young Oncologists Working Group. Between 2013 and 2017, he was member of AIOM National Board and since October 2019 he is AIOM National Secretary.
**AOR:**
In the last years, you published several studies pointing to the need to include quality of life (QoL) among the endpoints of clinical trials conducted in oncology. Why this choice?

**Massimo Di Maio:**
As a medical oncologist, I strongly believe that QoL and patient-reported outcomes have a crucial role both in clinical trials and in clinical practice. In 2017, we started working to a systematic review about the adoption of QoL in cancer clinical trials (1). I was convinced that such an analysis could have been important in denouncing, to the scientific community, the lack of attention to the QoL of patients in the development and approval of new treatments which, hopefully, can become new standard therapies. In addition, this kind of work, implying the screening and careful analysis of many hundreds of publications, could have been carried out only counting on the collaboration of many colleagues, and so I involved a number of young fellows attending the Specialty School in Oncology. All of them were enthusiast about the study. The added value of that experience, in my view, has been precisely to raise awareness on the topic, not only among the scientific community (once our paper has been published and discussed), but particularly among all the young colleagues who have been involved in the work. I am pleased to think that attention to quality of life and patient-reported outcomes for patients with cancer has been part of their training.

**AOR:**
What is the definition of patient-reported outcomes and what is their added value to clinical research?

**Massimo Di Maio:**
Any outcome evaluated directly by the patient and based on patient’s perception of a disease and its treatment is called patient-reported outcome (PRO). From this “general” definition, it is clear that the term PRO is an *umbrella term*, which can cover measures of symptoms, health-related quality of life, health status, adherence to treatment, satisfaction with treatment, and many other important domains. No need to specify that these instruments have a relevant role in oncology. Not only from a regulatory point of view, but also from a clinical point of view, the main goal of any anticancer treatment is to allow patients to live longer and/or to live better, so the point of view of patients is essential to evaluate the efficacy of new anticancer treatments. In recent years, progression-free survival (PFS) has been often adopted as primary endpoint in many trials, instead of overall survival (OS). When the experimental treatment demonstrates a benefit in PFS (that means in the instrumental control of the disease), PROs and QoL measures are particularly important to better define the real clinical impact of a treatment. However, I believe that even when the experimental treatment demonstrates a clinically relevant improvement in OS, PROs and QoL results are not useless and are still of interest, because they allow a more complete definition of benefits and harms associated with the treatment. I still think that in the era of precision medicine, the selection of the right drug for the right patient cannot neglect the opinion of the patients regarding what can be considered really right for themselves. I think that this is a fundamental part of a good tailored medicine.

**AOR:**
If you had only 5 minutes to convince investigators who are designing a clinical trial to include patient-reported outcomes among the endpoints, what are the main reasons you would emphasize?

**Massimo Di Maio:**
They should be the ones to convince me why NOT including PROs in their trial. Seriously, European Medicines Agency (EMA) helps me to provide this answer (2). EMA has provided a convincing list of reasons to include patient-reported outcomes in cancer clinical trials, and I personally agree with all of those 5 reasons. Firstly, PROs can provide a patient focused assessment of the burden and impact of disease, by understanding how a treatment impacts on patient functioning and well-being. This means “giving voice to the patient”, not rhetorically but substantially. Second, their analysis can add information on the clinical benefit of a therapy by complementing efficacy and safety data with patient-reported evaluation. Thirdly, PROs allow assessing the relationship/ agreement between clinical reported endpoints and patient-reported endpoints (and we have shown that symptoms and adverse events can be significantly underreported by clinicians). Fourth, PROs are essential in the non-inferiority trial setting: in this kind of trials, we accept to “sacrifice” part of the efficacy
obtained with the standard treatment, at the condition that the experimental treatment is preferable to the patient, so the measure of quality of life is essential to verify this assumption. Last but not least, in the clinical practice following the approval of the treatment, results of PROs obtained in the clinical trial can provide important information to facilitate more accurate future patient-physician communication in terms of the quality of life for the patient and the burden of treatment-related morbidities and disease-related patient impacts.

**AOR:**
How can QoL be formally included in the evaluation of treatment value?

**Massimo Di Maio:**
In recent years, stimulated by the debate about the rising prices of cancer drugs and about the flickering sustainability of the health system, scientific societies have tried to produce some instruments for the formal evaluation of treatment value. For me, it is not surprising that both the framework proposed by the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) magnitude of clinical benefit scale (MCBS) evaluating the value of anticancer treatments include QoL results among the parameters considered for the evaluation of study results. Briefly, in the ASCO framework a “palliation bonus” is awarded by the experimental treatment, if a statistically significant improvement in cancer-related symptoms is shown, and a “QoL bonus” is awarded if a statistically significant improvement in QoL is demonstrated (3). Similarly, in the ESMO MCBS, preliminary scores based on treatment efficacy can be upgraded when the experimental treatment demonstrates improved QoL or delayed deterioration in QoL (or substantial reduction in severe toxicity) (4). Consequently, there is no doubt that a complete evaluation of treatment value can be properly made only if the scientific community could evaluate QoL results at the same time of the other endpoints of a trial. Beyond the attention demonstrated by scientific societies, also regulatory agencies have made explicit their attention to QoL and PROs. Namely, both EMA and FDA have produced documents dedicated to the inclusion of PROs and quality of life in cancer clinical trials. These documents can easily be found on the web, and I believe this would be an interesting lecture for oncologists (2, 5). From my point of view, it means that regulatory agencies declare they will pay attention to these endpoints in the evaluation of treatments for the authorization for use in clinical practice. Until recent years, we must admit that this was not the case, at least for the vast majority of treatments: several analyses have shown that only a small proportion of cancer drugs approved for use in clinical practice have demonstrated a significant improvement in patients’ quality of life (6).

**AOR:**
You emphasize the importance of inclusion of patient-reported outcomes and QoL in clinical trials. However, this implies that investigators, and readers, become more familiar with specific methodology of analysis and presentation of results. Which are the most relevant issues in the methodology of QoL analysis?

**Massimo Di Maio:**
I have been involved in the analysis of QoL data for several clinical trials, and of course I am aware that the adoption of QoL among endpoints implies several methodological issues (1). First of all, when designing the trial and planning the study procedures, the choice of the correct QoL questionnaires and the best timing of administration are crucial. During the trial, all the efforts should be made to optimize the compliance to questionnaires (which depends not only on the patients’ motivation but especially on the attention paid by investigators): missing data can be a relevant problem, especially in diseases such as advanced lung cancer or pancreatic cancer or other advanced tumors characterized by a dismal prognosis, where the proportion of early treatment failures is often unfortunately not negligible. This can be a problem for the analysis, especially if the proportion of missing patients is unbalanced among study arms, considering that patients who do not fill in the questionnaires are mostly those who are getting worse (this phenomenon is called “missing not at random”), so we risk to catch a picture of patients’ quality of life that can be biased compared to the whole study population. Furthermore, as we have repeatedly shown in our analyses conducted in lung cancer (7), or in prostate cancer (8), or in colorectal cancer (9), methodology of analysis and presentation of results in the publications can be really heterogeneous. Many publications present mean scores at different time points or mean changes compared to baseline, but this analysis (which is useful to compare the “global” trends of different study arms), does not allow to understand how many patients...
considered less essential, because those trials will publication of QoL results of negative trials could be tant for the scientific community, we admit that the Although the results from negative trials are import-
ance (because they are collected during the treat-
analysis (because they are collected during the treat-
ment), it is a real scientific shame that QoL results 
clude QoL among endpoints. Furthermore, you 
cluded QoL among endpoints, there was often a delay in 
results, which are often not included in the primary study publication. How do you comment that finding?

Massimo Di Maio:
Yes, we found that, in a significant proportion of 
results were not included in the primary 
and there is a delay (of months, someti-
mes even of years) in the publication of QoL results 
. Many colleagues – both as investigators and as 
readers – are accustomed to this, and consider it 
normal that quality of life data should be present-
ed at congress and published abundantly after the 
main publication. To be honest, we were really dis-
appointed of this. If you consider that, by definition, 
QoL data are available at the moment of primary 
analysis (because they are collected during the treat-
ment), it is a real scientific shame that QoL results 
are often not included in the primary publication. 
Although the results from negative trials are impor-
tant for the scientific community, we admit that the 
publication of QoL results of negative trials could be 
considered less essential, because those trials will 
not imply the subsequent adoption of experimental 
treatments in clinical practice. On the other hand, 
there is no doubt that the absence of QoL data is 
particularly disappointing for trials with formally 
positive results. In fact, if the experimental treat-
ment has shown a benefit in terms of OS, QoL re-
results are helpful to define the trade-off between 
benefits and harms, helping to define the value, 
especially if the survival benefit is modest and the 
potential toxicity of the treatment is not negligible. 
QoL results are even more important when the in-
terpretation of the trial is based on a surrogate end-
point (such as PFS): in this case, we strongly believe 
that a patient-focused assessment should be crucial 
to define the value of a radiologically defined result. 
However, when discussing with Laura Marandino, 
Franco Perrone and all the other authors involved 
in our work, we have asked ourselves why QoL re-
results are often published later. There are several 
potential reasons: journals impose limitations of 
article length, and QoL results typically need much 
space to be adequately described, so a second pub-
lication appears a good solution. However, I believe 
that, in the era of electronic publications, the num-
ber of article pages should no more be a problem, 
and all the material that the authors consider rele-
vant could be published as supplementary material. 
Another issue could be the willingness of producing 
more than one publication for the same trial, also to 
allow visibility for a higher number of authors. My 
proposal, in this case, would be to submit the QoL 
paper as a simultaneous, companion paper to the 
same journal, and let the editor decide. 
There is a general agreement that publication of 
QoL results is relevant, and I strongly believe that 
their publication should be available along with the 
other trial endpoints. In this sense, an effort by au-
thors and editors for a complete and timely report-
ing of clinical trials, including all relevant outcomes, 
would allow an exhaustive evaluation of the bene-

AOR: 
In conclusion, what do you think will be the role 
of QoL and patient-reported outcomes in the 
years to come?

Massimo Di Maio:
In the editorial accompanying our 2018 paper in the 
Annals of Oncology, Lesley Fallowfield defined QoL a “Cinderella” outcome (10). I found that definition very fitting, because QoL has traditionally received subop-
Optimal attention, even in the setting of advanced cancer, where the attention to patients’ symptoms and to the burden of treatment toxicity should be very high. QoL has often been considered a topic for experts in the field, an interesting but all in all “superfluous” endpoint. From this point of view, I am glad to see that the importance of QoL results in the definition of treatment value, within a patient-centered approach, is definitely increasing. I really hope that, if we will repeat our previous analysis comparing the adoption of QoL in trials published in the last 5 years with the results we observed in the period 2012–2016, we will observe a significant improvement in the proportion of clinical trials adopting QoL and presenting results in the publication. And let’s be optimistic and believe that the results in the future 5 years will be even better. As I have repeatedly said in these years, all stakeholders (patients, researchers, sponsors, regulatory agencies and scientific journals) should encourage the inclusion of QoL among study endpoints, with a complete and timely reporting of QoL results in the publications.

ETHICS

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Authors’ contribution
MDM was involved in drafting the manuscript and revising it critically for important intellectual content, and gave final approval of the version to be published.

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REFERENCES


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