UNIVERSITÀ DEGLI STUDI DELL'AQUILA

DIPARTIMENTO DI MEDICINA CLINICA, SANITA' PUBBLICA, SCIENZE DELLA VITA E DELL'AMBIENTE

Dottorato di Ricerca in Medicina Clinica e Sanità Pubblica

Curriculum Medicina Clinica

XXXVI ciclo

Medium to long-term effects of the COVID-19 pandemic on colorectal cancer diagnosis, management and survival outcomes in Italy: an updated analysis of the real-world multicenter COVID-DELAY study

SSD MED/06

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a.a. 2022/2023

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1. Abstract

Background

As extended analysis of the COVID-DELAY study, we aimed to assess the impact of COVID-19 pandemic on diagnosis, staging and survival outcomes among patients with colorectal cancer (CRC) diagnosis performed in 2019, 2020, 2021, and 2022 years.

Methods

All consecutive newly diagnosed CRC patients referred to 11 Italian Oncology Departments between March and December 2019, 2020, 2021, and 2022 were evaluated. Access rate (number of patients/year), demographic characteristics, diagnostic and therapeutic temporal intervals (between date of symptoms onset, radiological and cytohistological diagnosis, treatment start, and first radiological evaluation), as well as first-line PFS and OS among metastatic patients, were assessed.

Results

Compared to 2019 (n=690), a reduction in new CRC cases in 2020 (n=564, -18.3%) was found, followed by a progressive increase in new CRC diagnoses in 2021 (n= 748, +8.4%) and 2022 (n= 756, +9.6%); a higher rate of TNM stage IV tumours was diagnosed in 2020 (35.4%) and 2021 (31.0%) compared to 2019 (29.6%), with a normalization in 2022 (26.4%) ($p<0.001$); a higher rate of patients performed diagnosis of CRC after access to first aid in 2021 (32.3%) compared to 2019 (25.0%) and 2020 (27.2%), with normalization in 2022 (26.3%) ($p=0.023$); a lower rate of patients has been discussed in multidisciplinary tumor boards in 2020 (35.6%) compared to 2019 (45.4%), 2021 (47.5%), and 2022 (55.0%) ($p<0.001$).

A significant difference between histological diagnosis and first oncological examination (median of 30 vs. 38 days, respectively, $p<0.001$), cytohistological diagnosis and systemic treatment start (median of 49 vs. 58 days, $p<0.001$), first oncological appointment and systemic treatment start (median of 14 compared to 16 days, $p=0.007$), treatment start and first radiological assessment (median 96 compared 105 days, $p=0.027$) between 2020 and 2021-2022 years, respectively.

After propensity score matching for year of diagnosis, mOS was significantly worse in 2020, 2021 and 2022 compared to 2019 (27.6 vs 24.8 vs not reached vs 38.9 months, respectively) ($p<0.001$). Concordantly, PFS was significantly worse with each passing year: 13.0 vs 11.1 vs 9.2 vs 7.2 months in 2019, 2020, 2021, 2022, respectively ($p=0.00027$). These results were confirmed at multivariate analysis.

Conclusions

A progressive normalization in the rate of new CRC diagnosis as well as TNM stage at diagnosis, in 2021 and 2022 compared to 2020 and 2019, was found. The increase of new CRC cases might have affected some diagnostic-therapeutic time intervals in 2021-2022 years compared to 2020. Significantly, pandemic years resulted independently associated to worse PFS and OS outcomes results compared to the pre-pandemic phase.

2. Introduction

From the first rumblings in Hubei province to its brakeless worldwide spread, Coronavirus Disease 2019 (COVID-19) has represented one of the worst pandemics of the modern era.

Italy was the first Western country to face COVID-19 outbreak, experiencing a severe increase in terms of new cases and deaths, particularly during the first pandemic wave. Mitigation efforts such as lockdowns' institutions until a complete reorganization of the National

Health System, including reallocation of crucial human and economic health resources toward COVID-19 patient care pathways, were carried out to limit pandemic incidence and mortality and to face this unprecedented scenario [1, 2]. This inevitably impacted on hospital's admissions for non-communicable diseases, hampering both inpatients and outpatients care.

As a consequence, many diagnostic and therapeutic services in non-COVID-19-related care activities such as cancer screening and surgery have been deferred or cancelled [3, 4].

According to national statistics, colorectal cancer (CRC) stands as the second leading cause of cancer death regardless gender [5]. However, the large-scale adoption of screening programs and the implementation in the clinical practice of multidisciplinary diagnostic-therapeutic pathways have significantly impacted on CRC prognosis [6].

In a preliminary experience of the COVID-DELAY study, a decline in colorectal cancer (CRC) diagnoses in 2020, paralleled by the rising incidence of CRC at an advanced stage compared to 2019 was found On the other hand, Italian Oncology Departments guaranteed the tightness of diagnostic-therapeutic pathways and access to care in CRC patients, mitigating the effects of COVID-19 [7].

Patients with cancer appeared at increased risk of contracting SARS-CoV2 infection and developing more severe disease course and sequelae alongside with an increased risk of death [8-11]. The risk of higher tumor burden in patients affected by metastatic CRC (mCRC), together with the above mentioned increased risk of death or sequelae might have limited systemic treatment effectiveness in term of survival outcomes during COVID-19 pandemic years.

SARS-CoV-2 universal vaccination and boosting of immunity, together with the enhancement of public health measures and improvement management of the disease, led to a significant improvement in COVID-19-related outcomes particularly in patients affected by hematological and solid malignancies [12, 13].

Poor data concerning the effect of COVID-19 pandemic on diagnostic-therapeutic pathways and survival outcomes during the vaccination and the post-emergency pandemic phase are available to date. The aim of the present analysis was to assess the effects of COVID-19 impact on diagnosis, staging and treatment outcomes of CRC patients diagnosed and managed in different Italian regions across all the pandemic years.

3. Materials and Methods

3.1 Study design and population

All consecutive newly diagnosed CRC patients referred to 11 Italian Oncology Departments between March and December 2019 (pre-pandemic phase), 2020 (acute pandemic phase), 2021 (vaccination phase), and 2022 (post-emergency pandemic phase) were evaluated within the COVID-DELAY study ("Evaluation of COVID-19 impact on DELAYing diagnostic-therapeutic pathways of cancer patients in Italy") [7]. Aim of the present analysis was to estimate the difference in terms of diagnosis and treatment from 2019 to 2022, by assessing total number of new diagnoses per year, and temporal intervals between date of symptoms onset, radiological and cytohistological diagnosis, first oncological appointment, treatment start and first radiological reassessment. Differences in patients and disease characteristics as well as in progression-free survival (PFS) and overall survival (OS) among patients affected by mCRC were also assessed.

Ethical approval to conduct this study was obtained by the respective local ethical committees on human experimentation of each participating center, after previous approval by the coordinating center ("Comitato Etico Regionale delle Marche—C.E.R.M.", Reference Number 2021 139). The present study complies with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws, and fulfills Regulation (EU) 2016/679 of the European

Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data.

Patients were included if they were 18 years or older, had histologically proven diagnosis of CRC performed between March and December 2019, 2020, 2021, 2022, received at least one type of oncological treatment (either surgery, radiotherapy, or systemic therapy) after diagnosis, and had available data about radiological diagnosis, cytohistological diagnosis, and treatment start. Patients with recurrent CRC, gastrointestinal (GI) metastases from cancer of a different organ, or GI malignancies other than CRC were excluded.

Temporal intervals between date of symptoms onset, radiological diagnosis, cytohistological diagnosis, first oncological appointment, treatment start, and first radiological reassessment of each patient with CRC diagnosis performed from March to December 2019, 2020, 2021, 2022 were computed and compared with each other. To avoid negative values, data of patients who had their CRC diagnosis after first oncological appointment (as per standard practice of referral Hospitals) were not included in the calculation of these specific temporal intervals.

Baseline (at diagnosis) data about patient, tumor and treatment characteristics were also retrieved from medical records and differences were analyzed.

Subgroup analyses were performed by investigating the study aims according to the regions (Northern, Central, Southern Italy) of the Oncology Department where patients with CRC were managed.

3.2 Statistical analysis

Descriptive statistics were used to report baseline patient, disease and treatment characteristics. Categorical variables were presented in the form of frequencies and percentages; while continuous variables by mean, standard deviation, minimum and maximum value (if normal/gaussian distribution); or using median and interquartile range

(if not normal/gaussian distribution). Differences between categorical variables were analyzed by exact Fisher test or chi-square, as appropriate, while differences between continuous variables were evaluated by Student T-test or Mann-Whitney U-test as applicable.

PFS was calculated starting from the first cycle of chemotherapy until patient's death or first-sign of disease progression or the last visit for patients who were lost-to-follow-up. OS was calculated starting from the first cycle of chemotherapy until patient's death or the last visit for patients who were lost-to-follow-up. Survival was calculated by Kaplan-Meier method and association with variables was assessed by log-rank test. Multivariate analysis was performed by Cox regression.

Multivariate analysis was performed by taking into account stratification factors that were described previously: sex, age with two different cut-offs (early onset: <50 years old, standard onset: 50-75 years old, elderly: >75 years old), regions of Italy (Northern vs Centre vs Southern), primary tumor sidedness (right vs left vs rectum), KRAS/NRAS/BRAF mutation (all wild-type vs BRAF mutant vs RAS mutant), MSI-H/d-MMR status (yes vs not), ECOG-PS at treatment start (0 vs 1 vs 2-3) and whether diagnosis was performed during emergency ward admittance (yes vs not).

Propensity score matching was performed by taking into account all the above mentioned stratification factors after being dichotomized (year of diagnosis 2019: yes vs not, sex: male vs female, Italian region: Centre vs not, BRAF mutation: yes vs not, RAS mutation: yes vs not, right-side tumor: yes vs vs not, ECOG PS 0: yes vs not, elderly age: yes vs not, early onset CRC: yes vs not, emergency ward admission at diagnosis: yes vs not, MSI-H/d-MMR status: yes vs not). Method used was "nearest", caliper was set at 2, ratio was set at 1.

The alpha level for all analyses was set to $p < 0.05$.

For all calculations we used IBM SPSS Statistics, version 26.0 (released 2019, IBM SPSS Statistics for Macintosh, version 26.0; IBM Corp., Armonk, NY, USA), MedCalc® Statistical Software version 19.7.2

(MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) and R statistical software (version 4.1.2) (with loaded packages matchIt, survival, survminer, logistf).

4. Results

4.1 Patients and disease characteristics

A total of 2758 patients affected by CRC at any stage were included in the present analysis (Figure 1).

Compared to 2019 (n=690), a reduction in new CRC cases was found in 2020 (n=564, -18.3%). On the other hand, a progressive increase in new CRC diagnosis was found in 2021 (n= 748, +32.6%) and 2022 (n= 756, +34.0%), compared to 2020.

Regarding tumour and patients' characteristics, a higher rate of TNM stage IV tumours was diagnosed in 2020 (35.4%) and 2021 (31.0%) compared to 2019 (29.6%), with a normalization in 2022 (26.4%) ($p<0.001$) (Figure 2).

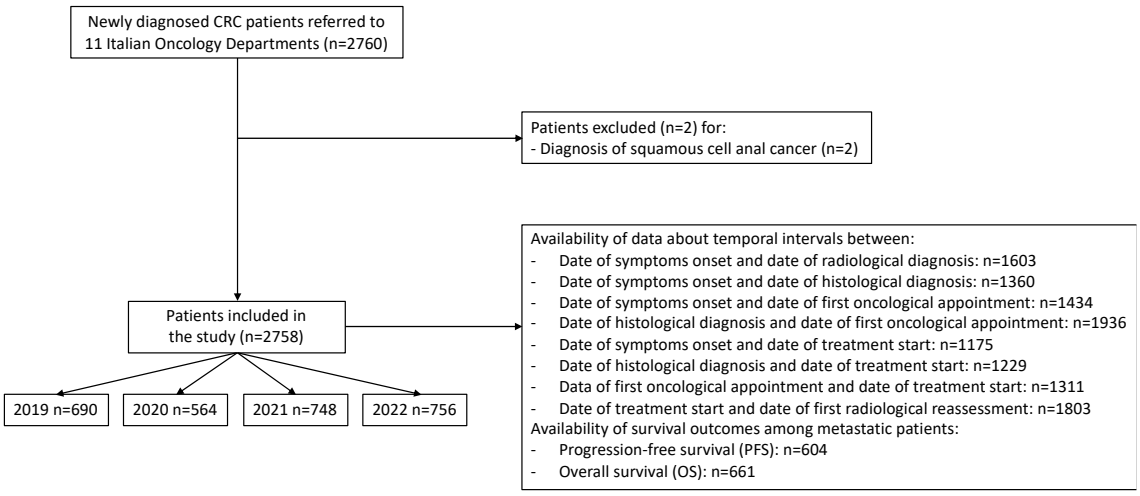


Figure 1. CONSORT diagram with patient's selection and disposition according to the availability of data concerning diagnostic-therapeutic temporal intervals and survival.

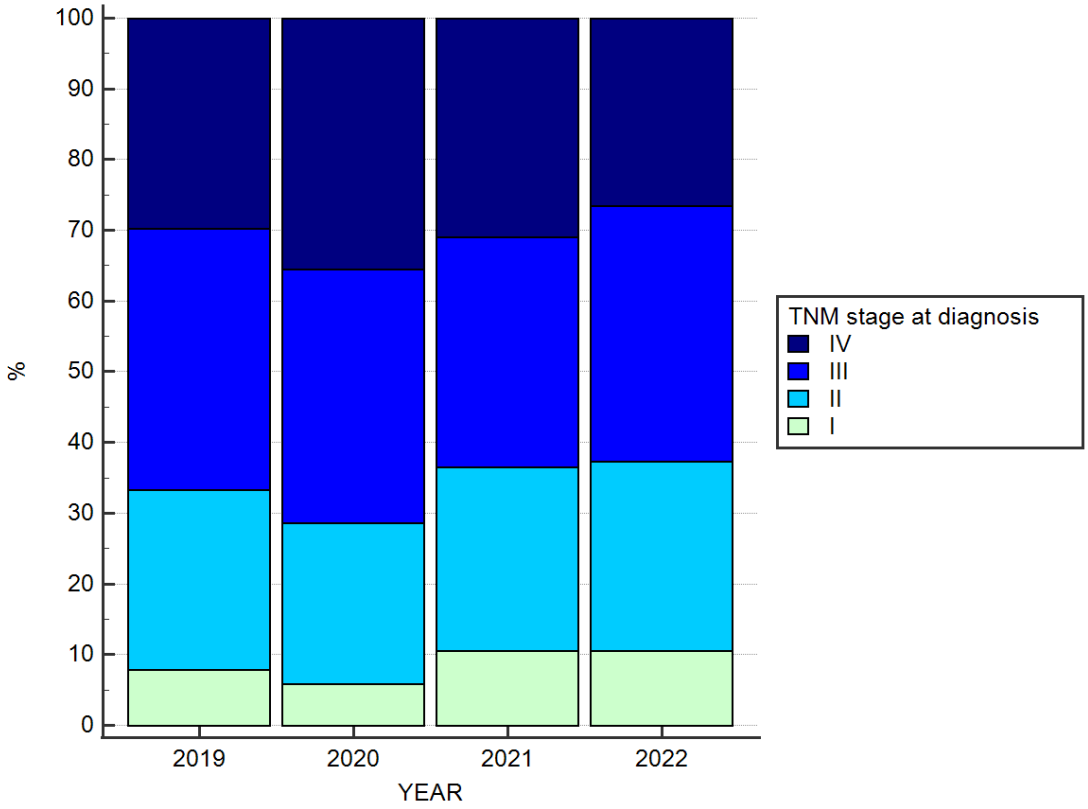
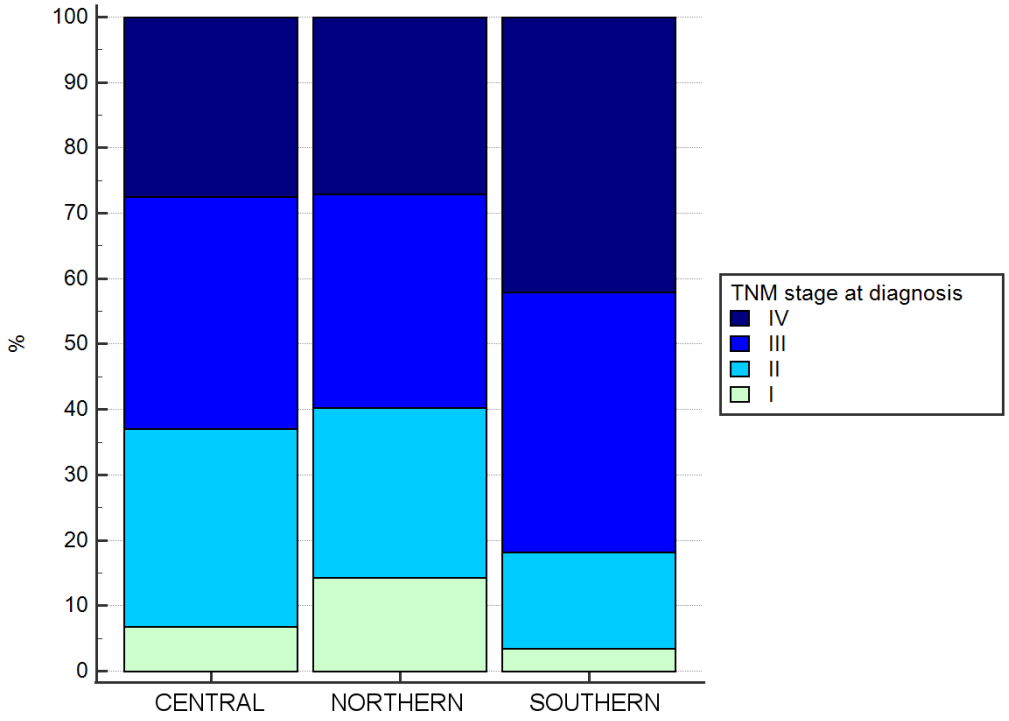


Figure 2. TNM stage according to year of diagnosis.

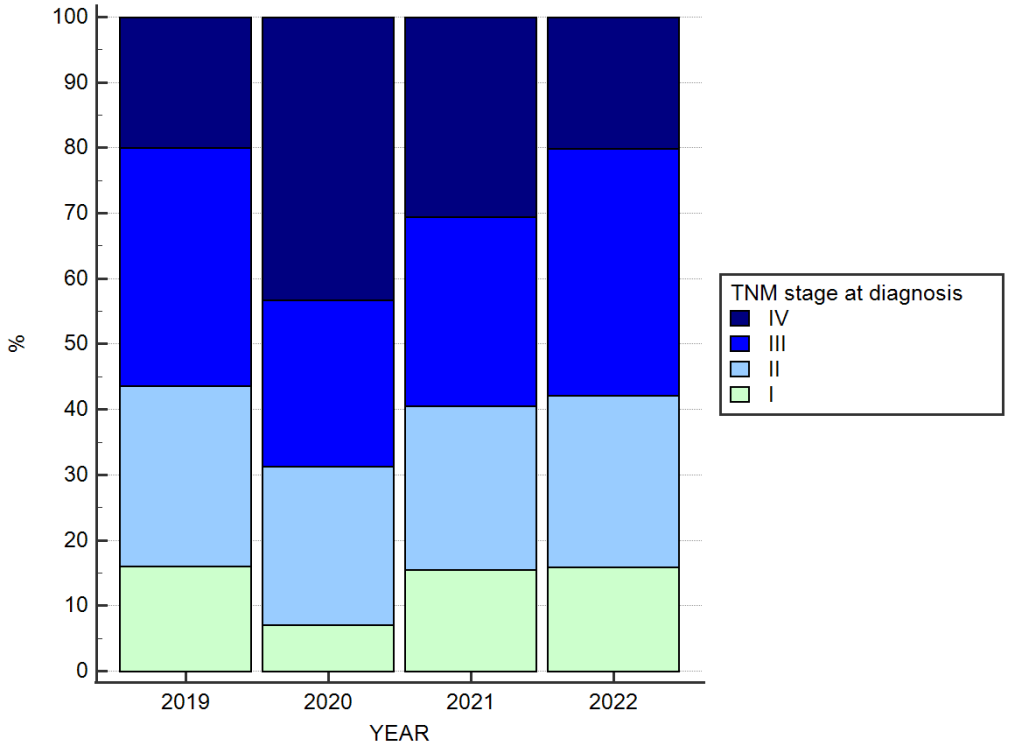
Focusing on TNM stage at diagnosis according to the different regions of Italian oncology departments, a statistically significant difference, regardless of year of diagnosis, was found. Particularly, compared to the Central and Southern regions, a higher rate of earlier CRC diagnoses was found in Northern Italy. Indeed, TNM stage I cases were 144/1004 (14%), 78/1136 (7%), and 20/564 (3%), meanwhile TNM stage IV cases were 271/1004 (27%), 312/1136 (27%), and 237/564 (42%) in the Northern, Central, and Southern Italy, respectively ($p<0.0001$) (Supplementary figure 1).

When regions were assessed separately, differences in TNM stage at diagnosis were also evident.

In Northern Italy, TNM stage IV diagnoses were 47/236 (20%), 73/169 (43%), 89/291 (30%), and 62/308 (20%) in 2019, 2020, 2021, and 2022 respectively ($p<0.0001$) (Supplementary figure 2).



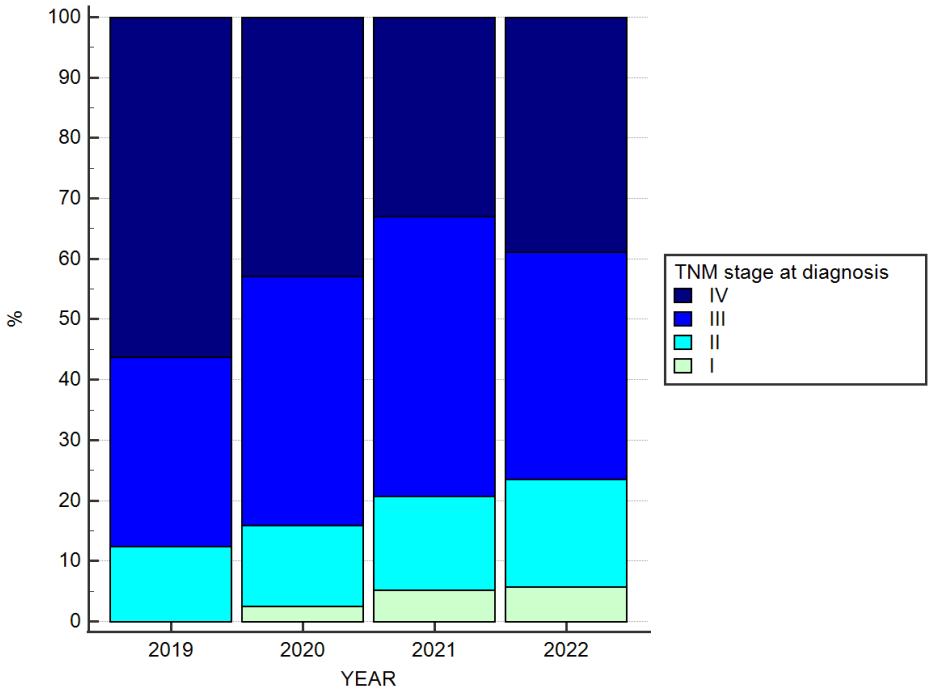
Supplementary figure 1. TNM stage at diagnosis according to Italian regions.



Supplementary figure 2. TNM stage at diagnosis according to year in Northern Italy

On the other hand, no statistically significant differences in TNM stage at diagnosis were found in Central Italy: TNM stage IV cases were 83/316 (26 74/%), 271 (27%), 80/266 (30%), 75/283 (75%) in 2019, 2020, 2021, and 2022, respectively (p=0.08).

Finally, a statistically significant change in TNM stage at diagnosis, was found in Southern Italy: TNM stage IV diagnoses were 72/128 (56%), 51/119 (43%), 57/173 (33%), and 61/157 (39%) in 2019, 2020, 2021, and 2022, respectively (p=0.0041) (Supplementary figure 3).



Supplementary figure 3. TNM stage at diagnosis according to year in Southern Italy

Intriguingly, a higher rate of patients performed oncological diagnosis after access to first aid in 2021 (32.3%) compared to 2019 (25.0%) and 2020 (27.2%), with normalization in 2022 (26.3%) ($p=0.023$). Overall, a lower number of patients has been discussed in multidisciplinary tumor boards in 2020 (35.6%) compared to 2019 (45.4%), 2021 (47.5%), and 2022 (55.0%) ($p<0.001$). Intriguingly, a higher rate of mucinous tumors was diagnosed in 2021-2022 (12.5-12.3%) compared to 2019-2020 (5.3-5.2%) ($p<0.001$), with a similar higher rate of dMMR/MSI-H in 2021-2022 compared to previous years (9.5-15.5% vs 7.6-7.9%, $p<0.001$). According to region, during 2021-2022 compared to 2019-2020 years, a lower rate of new cancer diagnoses was performed at the Oncology departments of the Northern Italy with respect to those of the Central Italy ($p<0.001$) (Table 1).

Characteristics	2019 N (%)	2020 N (%)	2021 N (%)	2022 N (%)	*p* value
Patients	690	564	748	756	
Sex					
Female	290 (42.0)	262 (46.5)	348 (46.5)	349 (46.2)	0.266
Male	400 (58.0)	302 (53.5)	400 (53.5)	407 (53.8)	
Age, years, median (range)	70 (28-95)	69 (21-92)	70 (26-94)	70 (27-96)	-
ECOG-PS at start of treatment					
0	298 (61.8)	269 (63.4)	356 (61.2)	340 (56.1)	0.353
1	156 (32.4)	131 (30.9)	190 (32.6)	216 (35.6)	
2	23 (4.8)	20 (4.7)	26 (4.5)	42 (6.9)	
3	5 (1.0)	4 (0.9)	10 (1.7)	8 (1.3)	
Sidedness					
Right	286 (42.8)	225 (40.2)	302 (40.5)	314 (41.6)	0.602
Left	297 (44.4)	275 (49.1)	353 (47.3)	340 (45.0)	
Rectum	86 (12.9)	60 (10.7)	91 (12.2)	101 (13.4)	
Tumor histology					
Adenocarcinoma	646 (94.3)	527 (94.3)	645 (86.8)	659 (87.2)	< 0.001
Mucinous	36 (5.3)	29 (5.2)	93 (12.5)	93 (12.3)	
Neuroendocrine cancer (NEC)	3 (0.4)	3 (0.5)	5 (0.7)	4 (0.4)	
Stage at diagnosis					
I	56 (8.2)	33 (5.9)	77 (10.5)	80 (10.7)	< 0.001
II	173 (25.4)	127 (22.7)	190 (26.0)	200 (26.7)	
III	251 (36.8)	201 (36.0)	237 (32.5)	271 (36.2)	
IV	202 (29.6)	198 (35.4)	226 (31.0)	198 (26.4)	
Diagnosis performed after access to first aid					
Yes	116 (25.0)	99 (27.2)	227 (32.3)	188 (26.3)	0.023
No	348 (75.0)	265 (72.8)	476 (67.7)	526 (73.7)	
Mutational Status					
RAS/BRAF wild-type	169 (54.3)	142 (49.8)	165 (47.6)	162 (50.2)	0.161
RAS mutant	116 (37.3)	119 (41.8)	149 (42.9)	118 (36.5)	

BRAF mutant	26 (8.4)	24 (8.4)	33 (9.5)	43 (13.3)	
MMR/MSI status					
pMMR/MSS	305 (92.4)	326 (92.1)	534 (90.5)	491 (84.5)	< 0.001
dMMR/MSI-H	25 (7.6)	28 (7.9)	56 (9.5)	90 (15.5)	
Treatment setting					
Neoadjuvant (including CTRT)	85 (12.5)	83 (15.0)	100 (14.9)	101 (14.0)	< 0.001
Adjuvant	182 (26.7)	169 (30.6)	202 (30.2)	247 (34.2)	
Metastatic	168 (24.6)	160 (28.9)	190 (28.4)	176 (24.4)	
Adjuvant post-metastasectomy (NED)	5 (0.7)	11 (2.0)	13 (1.9)	8 (1.1)	
Follow-up	241 (35.3)	128 (23.1)	161 (24.1)	190 (26.3)	
Best supportive care	1 (0.1)	2 (0.4)	3 (0.4)	0 (0.0)	
Radiotherapy					
Yes	77 (13.4)	75 (15.9)	96 (13.2)	96 (12.9)	0.475
No	499 (86.6)	397 (84.1)	631 (86.8)	647 (87.1)	
MTD discussion					
Yes	313 (45.4)	198 (35.6)	350 (47.5)	410 (55.0)	< 0.001
No	376 (54.6)	358 (64.4)	387 (52.5)	335 (45.0)	
Inclusion in clinical trials					
Yes	26 (4.1)	14 (2.7)	24 (3.2)	21 (2.8)	0.455
No	605 (95.9)	511 (97.3)	719 (96.8)	732 (97.2)	
Region according to Department site					
North	319 (46.2)	272 (48.2)	271 (36.2)	289 (38.2)	< 0.001
Centre	241 (34.9)	171 (30.3)	304 (40.6)	311 (41.1)	
South	130 (18.8)	121 (21.5)	173 (23.1)	156 (20.6)	

Table 1. Patients characteristics according to year of diagnosis.

P-values were calculated excluding unknown values. Abbreviations: ECOG-PS: Eastern Cooperative Oncology Group performance status; MMR/MSI: mismatch repair/microsatellite instability; pMMR/MSS: mismatch repair proficient/microsatellite stable; dMMR/MSI-H: mismatch repair deficient/microsatellite instability high; CTRT: concurrent chemo-radiation therapy; NED: not evidence of disease; MTD: multidisciplinary team.

4.2 Time Intervals

Looking at patients' management, a significant difference in terms of temporal interval between histological diagnosis and first oncological examination, histological diagnosis and systemic treatment start, first oncological appointment and systemic treatment start across the 4 years was found (Table 2). This variation was mostly led by a significant difference between histological diagnosis and first oncological examination (median of 30 vs. 38 days, respectively, p<0.001), cytohistological diagnosis and systemic treatment start (median of 49 vs. 58 day, p<0.001), first oncological appointment and systemic treatment start (median of 14 vs. 16 days, p=0.007), treatment start and first radiological assessment (median 96 vs. 105 days, p=0.027) between 2020 and 2021-2022 cohort, respectively (Supplementary table 1).

Time interval	2019 Median, days (IQR)	2020 Median, Days (IQR)	2021 Median, Days (IQR)	2022 Median, Days (IQR)	P value
Symptom onset/radiological diagnosis	25 (54)	20 (58)	21 (46)	25 (44)	*0.028*
Symptom onset/cytohistological diagnosis	31 (47)	28 (62)	27.5 (49)	25 (46)	*0.042*
Symptom onset/first oncological appointment	79 (63)	69 (65)	76 (62)	72 (63)	*0.126*
Cytohistological diagnosis/first oncological appointment	39 (37)	30 (30)	38 (32)	39 (36)	*<0.001*
Symptom onset/treatment start	99 (86)	91 (78)	98 (77)	90 (67)	*0.057*
Cytohistological diagnosis/treatment start	59 (42)	49 (43)	57 (44)	58 (34)	*<0.001*
First oncological appointment/treatment start	17 (20)	14 (16)	19 (19)	16 (15)	*0.042*
Treatment start/first radiological assessment	105 (97)	96 (87)	106 (96)	104 (56)	*0.181*

Table 2. Temporal intervals between date of symptoms onset, radiological diagnosis, cytohistological diagnosis, first oncological appointment, treatment start, and first radiological reassessment between 2019, 2020, 2021 and 2022. IQR, interquartile range. [a]Kruskal-Wallis H test comparing time intervals among them in 2019, 2020, 2021, and

2022 years. P values were calculated excluding patients with unknown values. Statistically significant (P < 0.05).

Time interval	2020 Median, Days (IQR)	2021-2022 Median, Days (IQR)	P value
Symptom onset/radiological diagnosis	20 (58)	23 (42)	*0.914*
Symptom onset/cytohistological diagnosis	28 (62)	26 (47)	*0.430*
Symptom onset/first oncological appointment	69 (65)	73 (63)	*0.323*
Cytohistological diagnosis/first oncological appointment	30 (30)	38 (33)	*<0.001*
Symptom onset/treatment start	91 (78)	94 (73)	*0.559*
Cytohistological diagnosis/treatment start	49 (43)	58 (38)	*<0.001*
First oncological appointment/treatment start	14 (16)	16 (18)	*0.007*
Treatment start/first radiological assessment	96 (87)	105 (81)	*0.027*

Supplementary table 1. Temporal intervals between date of symptoms onset, radiological diagnosis, cytohistological diagnosis, first oncological appointment, treatment start, and first radiological reassessment between 2019-2020 and 2021-2022**.** IQR, interquartile range. [a]Mann-Whitney U test comparing time intervals between 2020 and 2021-2022. P values were calculated excluding patients with unknown values. Statistically significant (P < 0.05).

4.3 Survival outcomes

659 stage IV patients were evaluable for OS analysis and 600 patients were evaluable for first-line PFS analysis. At a median follow-up time of 21.2 (95%CI: 19.5-22.8) months in the overall population, 432/600 (72%) patients progressed after first-line treatment and 261/659 (40%) patients have already died. Median follow-up time was 41.2 (95%CI: 39.0-43.4), 29.7 (95%CI: 28.4-31.1), 18.9 (95%CI: 17.9-19.8), and 7.0 (95%CI:6.1-7.9) months in the 2019, 2020, 2021, and 2022 cohorts, respectively.

In the overall population, first-line median OS (mOS) was 26.74 (95%CI: 24.4-30.8) months while first-line median PFS (mPFS) was 9.77 (95%CI: 9.2-10.5) months.

After stratification according to year of diagnosis, a statistically significant difference in mOS between mCRC patients diagnosed in 2019 (33.6 months, 95%CI: 29.2-42.7), 2020 (24.4 months, 95%CI: 20.3-30.0 months), 2021 (24.8 months, 20.5-26.5 months), and 2022 (18.0 months, 95%CI: 12.9-18.0) (p=0.0019) was found (Figure 3).

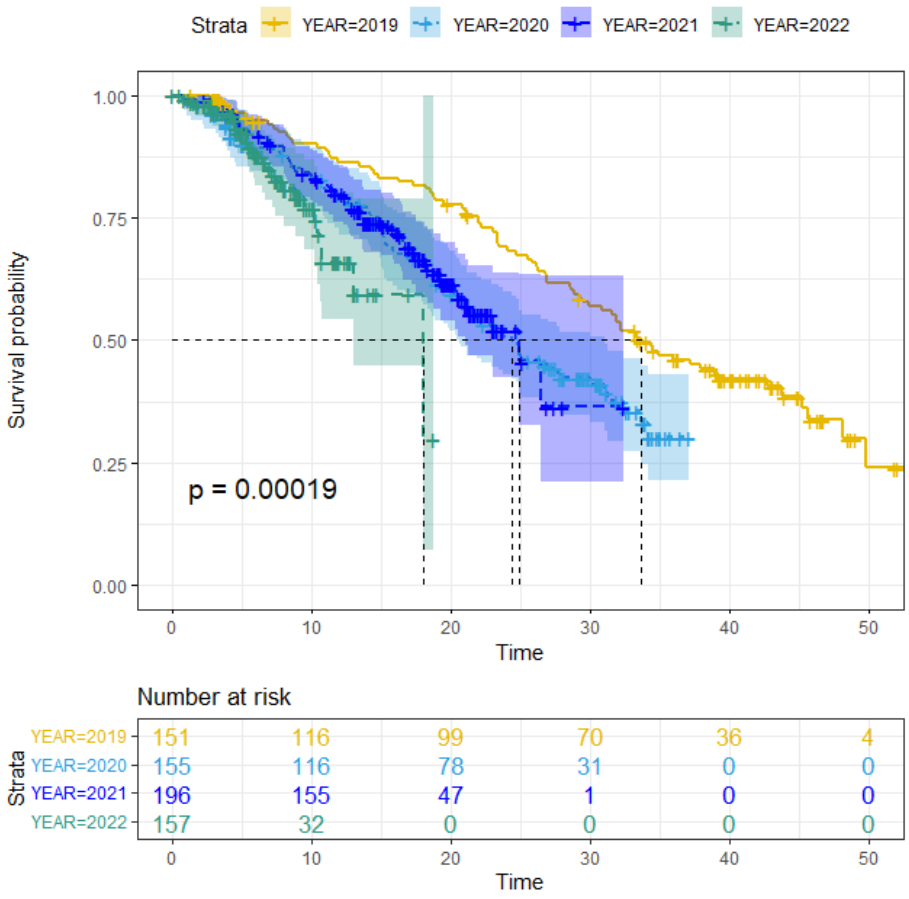


Figure 3. Kaplan-Meir curves for OS according to year of diagnosis.

Similarly, a statistically significant difference in mPFS between mCRC patients diagnosed in 2019 (12.7 months, 95%CI 10.2-14.4), 2020 (9.1

months, 95%CI: 8.1-9.7), 2021 (10.6 months, 9.0-11.8 months), and 2022 (7.3, 6.7-9.2 months) (p<0.0001) was found (Figure 4).

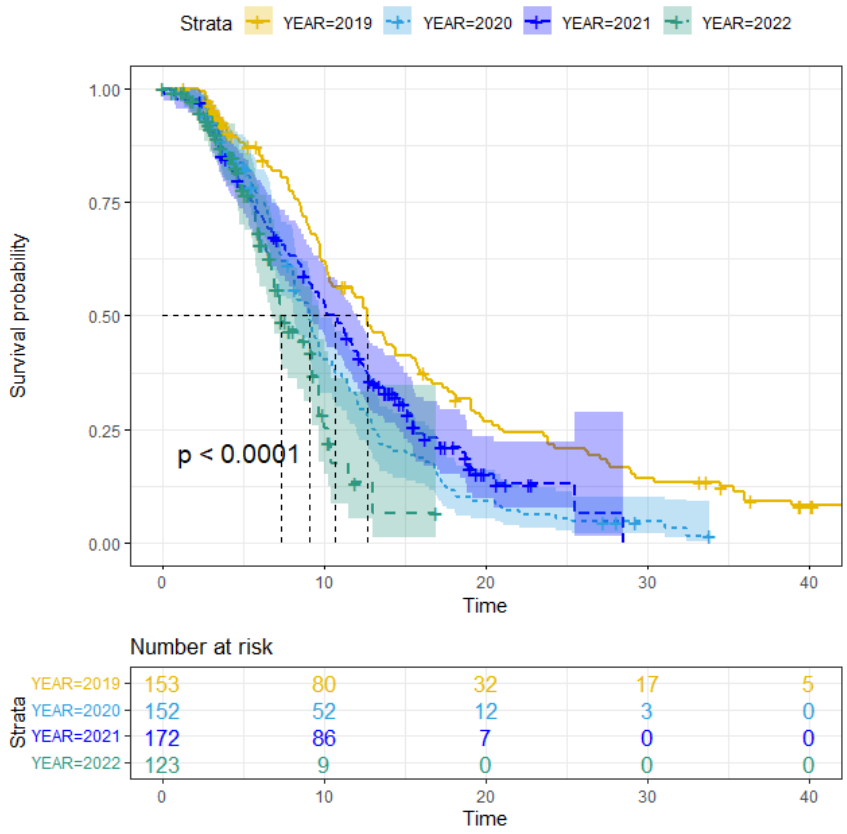


Figure 4. Kaplan Meier curves for PFS according to year of diagnosis.

Multivariate analysis for OS confirmed an independent negative prognostic role of year of diagnosis (worse OS in 2020, 2021, and 2022, each compared to 2019) with an incremental negative prognostic impact with each passing year. Intriguingly, an independent prognostic role of Italian region was found, while the prognostic role of ECOG-PS status and RAS mutations was confirmed (Table 3).

Concordantly, multivariate analysis for PFS confirmed the independent prognostic role of year of diagnosis, with worse PFS in 2020, 2021, and 2022, each compared to 2019. As expected, an independent prognostic role was confirmed for ECOG-PS as well as for BRAF and KRAS

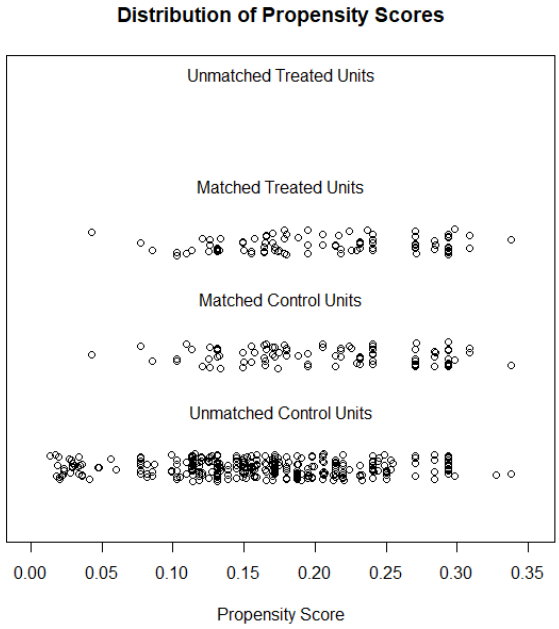
mutations. Intriguingly, an independent prognostic role according to Italian region categorization was found again. Early onset colorectal cancer patients (<50 years old) seemed to have better PFS compared to standard onset patients (Table 3).

Variable	Risk of death (OS)		Risk of disease progression/death (PFS)	
	Multivariable Co-HR (95% CI)	P value	Multivariable Co-HR (95% CI)	P value
Regions of Italy				
Central	1		1	
Northern	1.99 (1.31-3.0)	0.001	1.43 (1.08-1.91)	0.013
Southern	1.10 (0.75-1.6)	0.614	1.32 (1.00-1.74)	0.046
Year				
2019	1		1	
2020	1.76 (1.12-2.8)	0.014	1.90 (1.36-2.66)	<0.001
2021	2.29 (1.37-3.8)	0.002	1.73 (1.23-2.42)	0.002
2022	3.69 (1.83-7.4)	<0.001	2.8 (1.82-4.30)	<0.001
Molecular status				
RAS/BRAF wild-type	1		1	
BRAF mutant	1.44 (0.67-3.1)	0.345	2.38 (1.52-3.73)	<0.001
RAS mutant	1.68 (1.20-2.40)	0.003	1.56 (1.22-2.01)	<0.001
MMR/MSI status				
pMMR/MSS	1		1	
dMMR/MSI-h	0.81 (0.32-2.0)	0.644	0.50 (0.24-1.03)	0.062
Sidedness				
Left	1		1	
Right	0.80 (0.57-1.10)	0.929	1.00 (0.77-1.29)	0.966
Rectum	0.98 (0.58-1.60)	0.223	1.01 (0.69-1.47)	0.972
ECOG-PS				
0	1		1	
1	2.12 (1.52-2.9)	<0.001	1.56 (1.23-1.98)	<0.001
2-3	2.77 (1.28-6.0)	0.009	1.73 (0.95-3.16)	0.072
Age onset (years)				
50-75	1		1	
>75	1.09 (0.76-1.60)	0.622	0.99 (0.74-1.32)	0.954
<50	0.82 (0.41-1.60)	0.572	0.59 (0.37-0.94)	0.026
Diagnosis performed during access to first aid				
No	1		1	
Yes	0.94 (0.67-1.3)	0.747	1.11 (0.86-1.42)	0.062
Gender				
Male	1		1	
Female	1.03 (0.75-1.4)	0.857	1.03 (0.81-1.30)	0.838

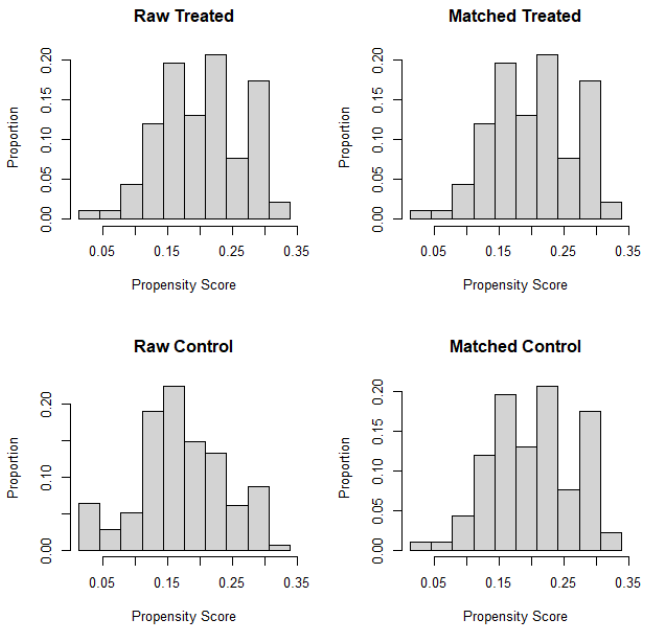
Table 3. Multivariate analysis for OS and PFS in the overall population.

After propensity score matching according to year of diagnosis (2019 vs 2020-2021-2022) out of 423 control units to be matched with 92

units of the 2019 cohort, 331 were discarded (Jitter plot and Histogram plot are shown in supplementary figures 4A and 4B).



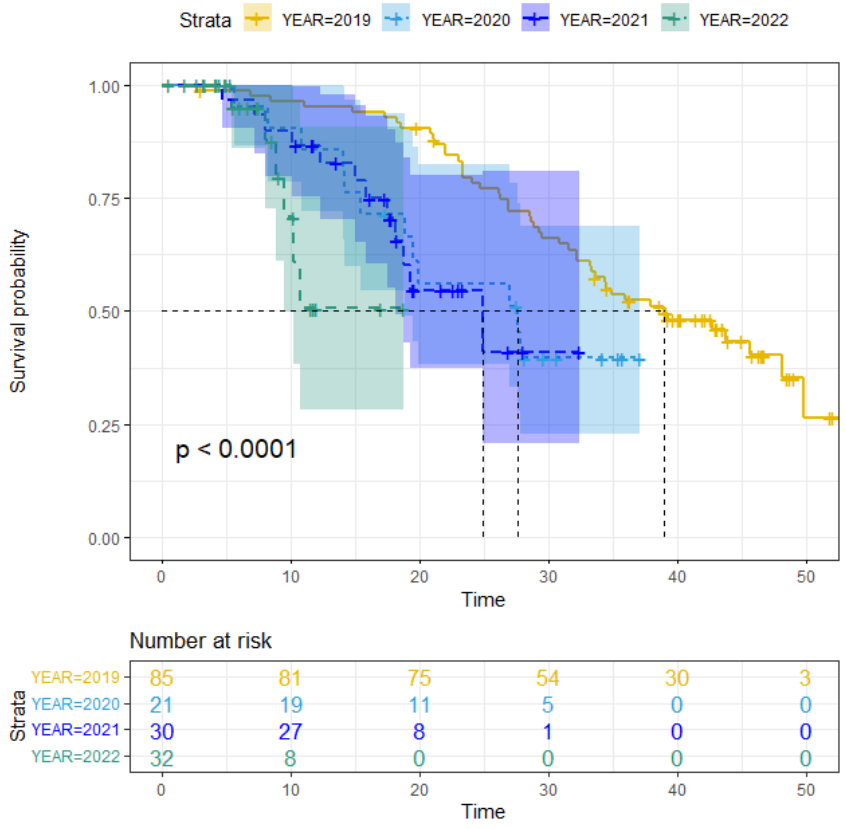
Supplementary figure 4 A. Jitter plot of the matched cohort.



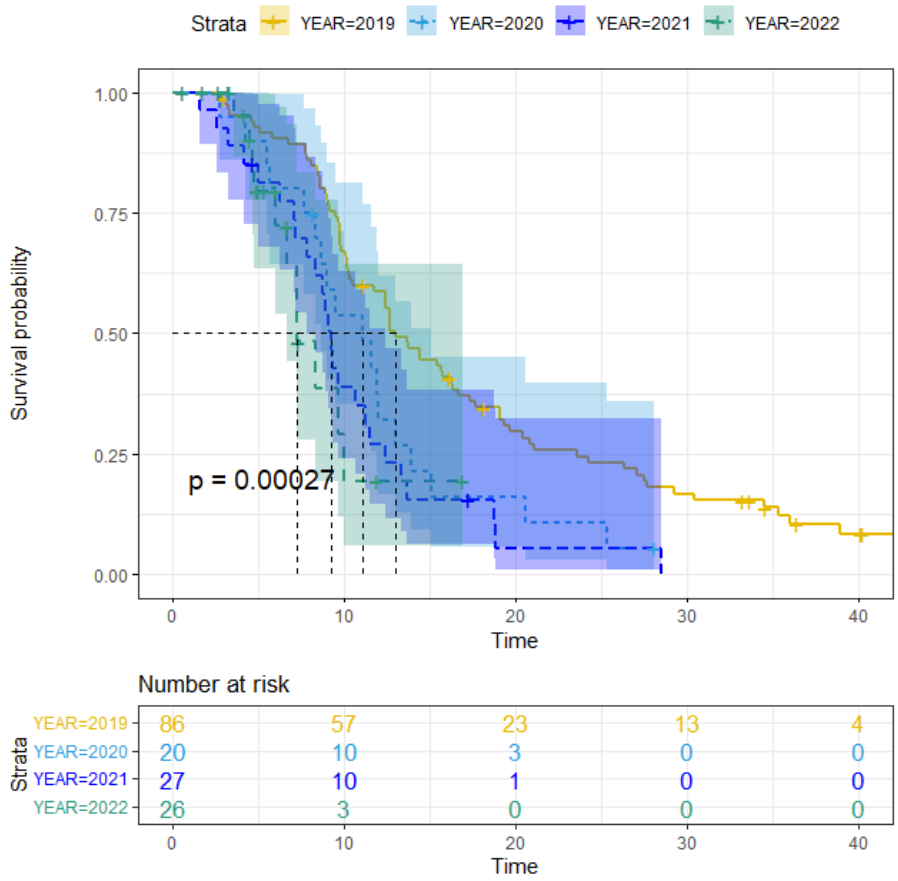
Supplementary figure 4B. Histogram plot of the matched cohort.

When survival analysis was performed in the matched cohort, mOS was still significantly worse in 2020, 2021 and 2022 compared to 2019 (27.6 (95%CI:15.36-27.83) vs 24.8 (95%CI:17.50-24.83) vs not reached (NA) vs 38.9 (95%CI:32.20-48.09) months, respectively) (p<0.001) (Supplementary figure 5).

Concordantly, PFS was also significantly worse with each passing year: 13.0 (95%CI:10.33-16.25) vs 11.1 (95%CO:7.70-12.99) vs 9.2 (95%CI:7.14-11.25) vs 7.2 (95%CI:6.02-10.03) months in 2019, 2020, 2021, 2022, respectively (p=0.00027) (Supplementary figure 6).



Supplementary figure 5. Kaplan-Meir curves for OS in the matched cohort.



Supplementary figure 6. Kaplan-Meir curves for PFS in the matched cohort.

5. Discussion

The COVID-19 outbreak has unprecedentedly changed the face of cancer care and permanently shaped the global health care landscape. With our country at the forefront of such unparalleled struggle, Italian oncologists were expected to lead their patients through the eye of the storm, weighing risks and benefits of giving cancer treatment compared to the chance of getting them infected with COVID-19 [14].

Furthermore, patients with cancer had to fight a struggle on multiple fronts: on one hand facing the fear of contracting COVID-19, with the risk of developing potentially severe or fatal complications, particularly in defined clinical settings [9-11]; on the other hand dealing with the

uncertainty of deferred elective oncological procedures as well as treatment plan discontinuations or adaptations.

Particularly in 2020, with a health care system close to collapse and limited experience-based guidelines and recommendations, medical oncologists' associations had to elaborate a prompt response. With these respect, contrasting measures have been adopted to effectively manage the crisis, such as patient-tailored reconsideration of treatment indication and schedule adaptation to reduce avoidable hospital admission, visits' conversion to telehealth encounters, and multidisciplinary board rearrangements following reallocation to COVID-19 units [15].

Under this point of view, despite the earliest establishment of experts' consensus and the implementation of these recommendations in daily clinical practice, the outcome of the efforts made to prevent diagnostic delays and the much-feared 'upstaging effect' were a matter of speculation and might have affected the subsequent years [15, 16].

Our analysis was thereafter intended to explore the effects on the expected cancer incidence as well as on cancer diagnostic-therapeutic pathways and survival rates, these diversions may have led to, during the post-pandemic phase.

In the first part of our analysis, a worsening drop in CRC diagnoses in 2020 compared to 2019 was confirmed [7]. This trend was in line with that reported by most of the 43 studies included in a recent systematic review investigating the effect on COVID-19 pandemic on the diagnosis and treatment of CRC [17]. Many factors might have contributed to this reduced number of diagnoses: lockdowns and fear of contagion might have deterred people symptomatic for CRC to ask for help and ultimately to undergo colonoscopy and instrumental assessment to properly diagnose and stage this disease. This fact might have led to late CRC diagnoses for patients who were symptomatic and thus a higher risk of larger tumor burden and more advanced disease at the time of diagnosis. Furthermore, this would justify the higher rate of

new diagnoses after first aid access in 2021, a results which is consistent with previous findings [17]. On the other hand, as screening programmes were suspended during the pandemic, CRC screening performed by fecal immunochemical test followed by colonoscopy was also temporarily halted: this might have led to a reduction in the number of early CRC diagnoses, mainly in the group of patients who were asymptomatic for this disease.

Within the present updated analysis, we highlight a worrying overdrop in terms of new CRC diagnoses during the vaccination phase and the post-emergency pandemic phase. Most strikingly, a significantly higher incidence of late-stage compared to early-stage CRC diagnoses in 2021 as well as in 2020 compared to 2019 was found, with a trend toward normalization in the post-emergency pandemic phase. It is easy to hypothesize this would be the number of patients who were so symptomatic they could not avoid to ask for help and who would be diagnosed with metastatic disease involvement. Indeed, if we look at what happened in the following years (2021-2022) the number of CRC diagnoses increased more due to a higher number of patients with early stage disease, rather than a net increase of the number of patients with metastatic disease. Taken together, these findings are consistent with data at national level and would indicate a gradual return to normality after a setback of the Italian healthcare system with respect to screening and diagnostic ability, alongside with a certain reluctance of many patients to seek health care in crowded healthcare centers, during both acute pandemic and vaccination phase [5, 18]. Interestingly, this could also explain the marked differences in stage at diagnosis that could be observed by comparing different geographical areas of Italy. If we assume that CRC screening should be considered an effective tool for early diagnosis of CRC, we would have expected that suspension of screening programmes would have the greatest impact on those areas where compliance with screening was the highest. Indeed, data from Italian Osservatorio Nazionale Screening (CIT) showed that adherence

to CRC screening was around 40.5% in 2019, compared to 34.1% in 2020 and 38.7% in 2021 [19]. However, marked differences between Italian regions were found. Indeed, from 2019 to 2020, compliance with screening programmes in Northern, Central and Southern Italy decreased from 49.4% to 46.8%, from 34.8% to 27.2%, and from 25.7% to 15.8%. Since the detection rate for cancer usually ranges around 0.08-0.2%, it can be expected that the decrease in early diagnoses would be more marked in Northern Italy compared to Central and Southern Italy, as our data seem to suggest.

Despite the hard times, our results further proved that Italian Medical oncologists met the challenge of preventing cancer patients from being left orphan of care. Indeed, no particular leakage in the management system of CRC patients emerged in terms of temporal intervals of the diagnostic-therapeutic pathway. Paradoxically, a reduced time was found in terms of some temporal intervals during 2020 compared to 2019 (i.e. between cytohistological diagnosis and first oncological examination, first oncological appointment and systemic treatment start) and, sometimes, compared to 2021 and 2022 years. At least in part, this might be related to the reduced number of new cancer patients diagnosed in 2020, easing the pressure on a pandemic distressed system and accelerating patients' encounters compared to 2019 as well as to 2021 and 2022 years. Additionally, the late-stage presentation shown after COVID-19, generally precluding a surgical approach, might have hastened the referral to medical oncologists. Moreover, this unexpected and positive trend in 2020 patients' management might have also been related to the extensive use of telemedicine and supported by the firm resilience of health care providers, as demonstrated by multiple resources [14, 20, 21]. On the other hand, the consistent increase of CRC cases might have affected some diagnostic-therapeutic time intervals during the vaccination and post-emergency pandemic phases compared to pandemic phase.

With the multidisciplinary tumour board (MTB) approach representing the best practice in management and decision making for cancer patients worldwide [22], COVID-19 pandemic limitations have imposed technical, financial and relational issues [23-25]. Intriguingly, after an initial setback of multidisciplinary discussion of CRC patients with a significant decrease in the rate of the cases reviewed in 2020 compared to 2019, the activity of MTBs progressively improved up to even exceed the pre-pandemic numbers. Of course, the introduction of properly regulated videoconferences as an alternative form of communication among medical professionals in routine MTB, while reducing the need of traveling time to conference rooms, might have helped to preserve and increase the rate of CRC patients cases properly shared and discussed.

COVID-19 pandemic triggered a brisk contraction of clinical research in Italy and globally [26, 27]. This drop in patient recruitment has been related to the decreased ability of clinical, support and preclinical units in providing nonessential activities and to the reallocation of resources to more critical services and trials [28]. With regard to the Centres involved in the present study, no statistically significant difference in terms of rate of patients enrolled in clinical trials across years from the pre-pandemic and the post-emergency pandemic phases was found.

One of the most interesting finding of our analysis is that concerning the alarming worsening of prognosis of patients with stage IV CRC during SARS-Cov2 pandemic years: despite the introduction of novel treatment modalities for patients with stage IV CRC in the last years (i.e. rechallenge or reintroduction with anti-EGFR for liquid biopsy proven RAS wild-type patients [29], encorafenib plus cetuximab treatment for BRAF V600E mutated patients [30, 31], and immune checkpoint inhibitors for patients with MSI-H/d-MMR metastatic CRC [32, 33]), both first line PFS and OS were increasingly worse with each passing year. This negative prognostic effect was confirmed after multivariate analysis and matching for all those stratification factors

that are usually considered having an impact on both PFS and OS (tumor sidedness, RAS and BRAF mutational status, ECOG PS at treatment start).

There might be a few explanations of this. At least in part, the higher risk of disease progression and death during the pandemic years might be related to changes in treatment plans, including changes to less effective systemic regimen in order to limit the risk of particularly hematological, treatment-related adverse events, as well as to the lower dose intensity of anticancer drugs which the pandemic phase might have led to (i.e. treatment discontinuation because of COVID-19 infection, limited access to day hospitals, reducing of day hospital "seats" for those patients undergoing to palliative chemotherapy, and so on) [15, 17, 34, 35]. Indeed, we observed that the same treatment modalities that were used in first-line setting did yield significantly worse outcomes after 2019, thus suggesting that something related to how treatment was performed might be responsible for the reduced effect.

Even though the negative impact on oncology wards and inpatient clinic activity was massive, the reduction in activity of surgical wards was even more marked. CRC prognosis is highly dictated also by radicality and quality of surgery, as previous studies have suggested. Indeed, primary tumor resection even in the metastatic disease setting and surgical management of oligometastatic disease are staple measures that have contributed to increasing overall survival of patients with mCRC. Indeed, while median overall survival of patients who receive best medical treatment options nowadays is estimated to be around 30-33 months, it easily ranges around 60-70 months for patients who undergo surgical resection of the primary tumor and metastases [36, 37]. Despite that, we could not prove this: the proportion of patients with stage IV diagnosis that underwent surgical resection of the primary tumor were 60% in 2019 vs 67% in 2020 vs 82% in 2021 vs 76% in 2022. This would seemingly suggest that, despite all limitations to

surgery in the pandemic years, the number of metastatic patients that were able to receive primary surgery was not reduced with each passing year. Resection of metastatic sites in this unselected population was 2-3% and was maintained the same throughout the years.

Another factor that might explain this reduced life expectancy is the one linked to greater tumor burden at diagnosis, as later diagnosis might mean increased size of the tumor at the time of discovery. There is no official consensus concerning how to reliably and reproducibly assess the size of tumor involvement and this might partly explain why this information is usually lacking in most analyses. However, everyday clinical practice easily shows that "bulky" tumor masses might have entirely different impact on patients' prognosis also based on metastatic site of involvement as in liver vs lung vs peritoneum vs others.

It is important to underline that the shorter follow-up time and the relatively low number of death events in the 2021-2022 compared to the 2020 cohort might have affected OS results and comparisons.

Since the present study represents the joint effort of a nationwide cooperation, it also accounts for regional variations in response to COVID-19 pandemic, including geographic distribution and local governments' crisis management. Interestingly, the higher reduction in terms of new CRC diagnoses between 2020 and 2019 was found in the regions of Northern Italy compared to Centre Italy, with a rebound effect in the post-emergency pandemic phase. These findings should not surprise since Northern Italy was committed first by COVID-19 pandemic in 2020.

We acknowledge that our work has potential limitations as a retrospective investigation. In the present study patients with recurrent disease were excluded in order to analyze an homogeneous sample of new CRC diagnoses and to avoid potential biases related to the oncological management during the follow-up period for patients with previous CRC. This decision could be considered a potential limitation of the study, since COVID-19 might have equally affected on diagnosis

and treatment of CRC relapse. Moreover, in the present updated analysis, regions from Southern Italy were not particularly represented. Neverthless, as the cooperative effort of a multicentred national collaboration, our data provide a valuable and through insight on cancer care across three years after COVID-19 pandemic outbreak. Moreover, differently from informatics data analysis from National Cancer Registries, our real-world study, through the analysis of medical records of 1845 patients, is less affected by potential reporting biases during the frenetic times assessed.

6. Conclusions

Gathering together all findings, our study confirmed the good outcome of the challenges tackled by Italian Oncology Departments to ensure the tightness of diagnostic-therapeutic pathways and mitigate the effects of COVID-19 across the crucial years of the pandemic. Significantly, pandemic years resulted independently associated to worse PFS and OS outcomes results compared to the pre-pandemic phase.

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