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# Age of Less than Forty Years Seems Not Be an Independent Factor for Poor Prognosis in Patients Undergoing Surgery for CRC

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## Abstract

**Introduction:** Colorectal cancer (CRC) is typically diagnosed in adults over 50 years of age, with overall incidence rates gradually declining. Only a small percentage of cases is seen in the younger population, but a particular peak is noticed in adults under the age of 40. However, an opposite trend of incidence is seen in this young population. It remains unclear if the prognosis of young CRC patients differs from that of the average-age CRC population.
The primary objective of this study was to compare overall survival (OS) and disease-free survival (DFS) between adults 40 years and a matched population >40 years, treated with curative-intent surgery for CRC (metastatic or not).

**Materials and Methods:** This retrospective study included patients who underwent curative-intent surgery at Institut Jules Bordet (IJB) for primary non-metastatic or metastatic CRC between 2007 and 2019. 31 patients ≤40 years and 62 patients >40 years were matched (1:2) according to established risk factors affecting OS and DFS. Survival curves illustrated the comparison of survival in these two groups, and eventual differences were calculated using the Lee, Wei and Amato (LWA) model.

**Results:** Median OS and DFS are respectively 46.6 and 16.3 months for patients ≤40 years and 66.4 and 13.1 months for patients >40 years ($p>0.05$). All young patients presented with abdominal symptoms before undergoing colonoscopy, whereas 62.5% of non-metastatic and 19.57% of metastatic patients >40 years were diagnosed on screening colonoscopy ($p<0.05$). In the metastatic group, younger patients presented more weight loss ($p=0.0013$) and constipation ($p=0.04$) at diagnosis.

**Conclusion:** Patients with early-onset metastatic or non-metastatic CRC who underwent curative-intent surgery had similar OS and DFS to patients >40 years when there are matched for predictive factors.

**Keywords :** Colorectal Cancer; Young; <40 Years; Outcomes; Symptoms

## Introduction

Colorectal cancer (CRC) is one of the most frequently diagnosed cancers globally, representing the second leading cause of cancer deaths among men and women combined [1]. CRC is considered mainly as a disease of the elderly and rather seldomly associated with younger adults [2,3].

Although, the overall incidence rates have been gradually declining over the past decades, notably in the United States. These findings are mainly due to the generalization of screening programs and subsequent early intervention for pre-cancerous lesions. However, these trends are solely seen in older persons and seem to mask the rising incidence of CRC cases in adults <55 years (by 1,8-2,2% annually). From 2001-2016, the median age of diagnosis of CRC has dropped from 72 to 66 years. The occurrence of most cases remains, however, in the age group above 50 years. The proportion of early-onset colorectal cancer (EOCRC) cases newly diagnosed in 2020 was estimated to represent about 12% of all CRC cases in the United States [4]. Since 2018, CRC became the second leading cause of cancer death in men aged 20-39 years, surpassing leukaemia. In addition, CRC is the leading cause of cancer death in men aged <50 years. These findings underline the increasing trends in CRC in these age groups [5].

Among adolescents and young adults (AYA), the most common sites of cancers vary considerably by age. The American Cancer Society (ACS) established the 2020 estimates of leading sites of new cancer cases in AYA (both sexes combined); CRC appears to be one of the most diagnosed cancers in adults aged 30-39 years [6].

The same tendency is described in Europe, with a particular peak in the age group 20-39 years [7].

The definition for the early-onset CRC (EOCRC) remains a subject of controversy and no precise cut-off age has been determined. Furthermore, there are considerable disparities regarding the prognosis of patients below the average screening age, with outcomes reported as worse, similar or even a more favourable compared to older patients [8].

The young onset-age of CRC is often associated with familial syndromes, such as familial adenomatous polyposis (FAP) and Lynch syndrome. These patients are particularly known to be at risk of CRC and hence submitted to an early screening. Thus, the vast majority of cases remains sporadic with no known predisposing genetic risk factor. This latter group is often described as a distinct entity compared to older patients since the stage at presentation is often advanced and associated with a more aggressive disease course (poor differentiation, distal location, early metastasis) [9].

Belgium is one of the many countries where EOCRC are rising (annual percentage change of + 3-4%, in CRC incidence in adults aged 20-39 years, from 1990 to 2016) [4]. The average age at diagnosis of CRC is 70.3 and 71.9 years for males and females, respectively. In 2018 there was a total of 7860 new cases of CRC registered in Belgium, counting 165 persons in total under the age of 40 years, representing 2% of new CRC cases diagnosed that year [10,11].

The primary objective of this study was to determine if there is a significant difference between survival rates of CRC patients younger than 40 years in comparison to those older than 40 years of age.

## Patients and Methods

### Study design and ethics

This was a retrospective cohort study of all patients treated with curative intent surgery for a primary non-metastatic or metastatic CRC at Institut Jules Bordet (IJB) between 2007 and 2019. The study was approved by the institutional Ethical Review Committee (CE3008).

### Primary objective

The study was designed to investigate the survival outcomes (OS and DFS) of early-onset colorectal cancer patients, defined by the cut-off age of 40 years and prior, in comparison to CRC patients older than 40 years.

### Population

Case records of patients ≤ and >40 years, who underwent curative-intent surgery at IJB for a primary or metastatic CRC, were evaluated. Patients were identified using the Cancer Registry of IJB. Details of the demographics, symptomatology, risk factors, family history and histopathological features were collected using the electronic patient's files system (Oribase).

All patients were classified according to their age at diagnosis (≤40 and >40 years). Furthermore, they were divided into two groups depending on their status at the time of surgery ("non-metastatic" or "metastatic").

The target group of this study were EOCRC patients defined as being ≤40 years at the time of diagnosis. The second group consisted of CRC patients diagnosed at >40 years. EOCRC patients were matched (1:2) with patients >40 years old accord-

ing to significant and well-established risk factors affecting OS and DFS. Exclusion criteria were patients who underwent any surgical procedures performed without curative intent and/or patients for whom no matching was possible.

### Matching variables

Each EOCRC patient was matched with two older CRC patients on variables considered risk factors determining OS and DFS (Supplementary material, Table 1s). Non-metastatic patients were matched by primary tumour location, pTNM stage, histological type, tumour differentiation, lymphovascular and perineural invasion and preoperative tumour markers (CEA and CA19.9).

Metastatic patients were matched by primary tumour location, synchronous or metachronous metastasis, preoperative tumour markers (CEA and CA19.9) and site of metastasis. Patients with peritoneal metastasis (PM) were furthermore matched by PCI score and those with liver metastasis (LM) by the number and size of metastasis at diagnosis.

This matching process allowed us to stratify patients of the two age groups according to specific disease patterns and, in fine, to compare patients with similar conditions.

### Selection of EOCRC patients

The Cancer Registry of IJB was used to identify patients by applying the following criteria: tumour location (colon, rectosigmoid junction, rectum, anus/rectum), diagnosis of primary tumour between 01/01/2007 and 31/12/2019, patients aged <41 years. Inclusion criteria included: primary CRC and metastatic (synchronous or metachronous) CRC eligible for curative-intent surgery. Exclusion criteria included: inoperable patients, palliative care, second primary tumours, pseudomyxoma, histological types of tumour such as carcinoid, gastrointestinal stromal and neuroendocrine tumours.

### Selection of patients >40 years

For each patient 40 years, we identified two patients with the same characteristic factors for OS and DFS. Patients >40 years were identified using the cancer registry of IJB. The same inclusion and exclusion criteria were used but starting at the age ≥41 years.

### Statistics

Medical information was encoded anonymously into a database using Microsoft Excel spreadsheets. Descriptive data were presented through the forms of means ± standard deviation (SD) and of medians (Min-Max) according to the distributions (Normal or not). For comparison of variables between the two age groups, the « Student » test or the « U test of Mann-Whitney » was used for continuous variables based on their distribution (Normal or not) and the « Chi-2» test was used to compare the proportions regarding the groups of patients. A P-value of <0.05 was considered statistically significant.

DFS was defined as the time from the first surgery (curative-intent) until the date of the first occurrence of one of the following events: cancer relapse (local recurrence, distant recurrence) or death (of any cause). OS was defined as the time from diagnosis until the date of the latest news or death of any cause. The Kaplan-Meier method was used to generate survival curves. As the data are paired, there was a dependence among failure times on the same pair. Therefore, the use of the log-rank test and the Cox proportional hazards model (to determine if there is a significant difference between the two groups) should be avoided. One helpful solution was the marginal hazard approach (LWA) which takes into account this dependency.

## Results

### Patient and disease characteristics

We identified 33 eligible patients in the institutional cancer registry. After applying inclusion and exclusion criteria for CRC patients >40 years of age, we found 62 suitable patients eligible for matching criteria. Two EOCRC patients were excluded for not having found a suitable match (rare histotypes of CRC). Finally, sixty-two patients >40 years old were found eligible for matching criteria with the 31 EOCRC patients (≤40 years). The flowchart is reported in Figure 1.

To substantiate our approach, we performed a statistical analysis of all variables that were matched between the two age groups (Table 1 and 2) and no significant difference was noted. These findings reflect an appropriate matching that enables us to compare patients with similar risk factors. Further descriptive data that included clinical, pathological and molecular features were summarized in Table 1 for non-metastatic patients and Table 2 for metastatic patients.

Of the 93 patients, we had 24 non-metastatic and 69 metastatic patients. Among the latter, 8 (25.8%) non-metastatic and 23 (74.2%) metastatic patients were younger than 40 years.

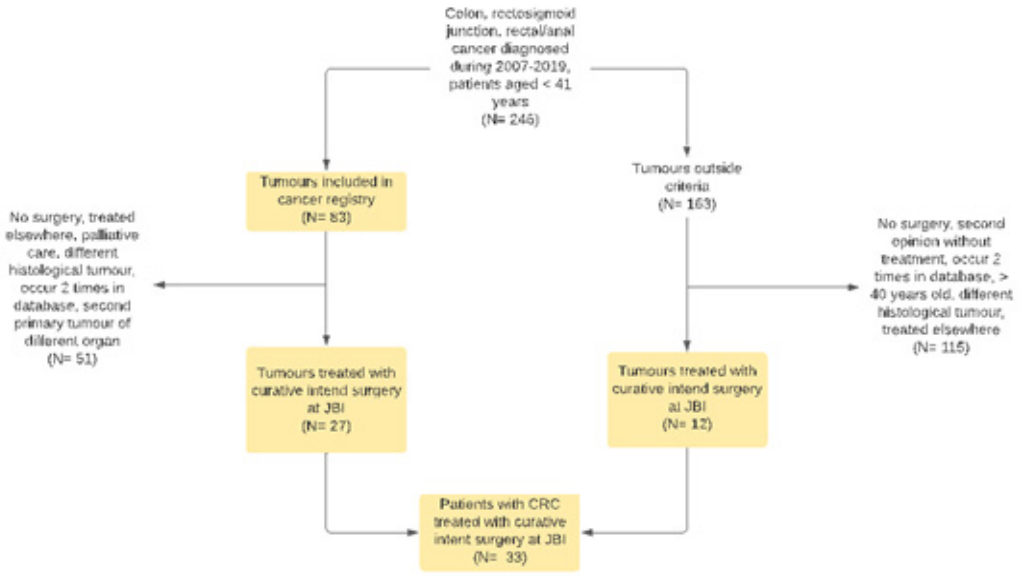



**Figure 1:** Patient's flowchart

| Non-metastatic groups | | | | |
|---|---|---|---|---|
| **Characteristics** | **Patients < 40 years (N=8)** | **Patients 40 yean (N=16)** | **Total (N=24)** | **P** |
| **Average age**<br>**Gender** | 34.75 (SD= 3.12) | 63.86($D=7.56) | | <0.001<br>0.6792 |
| Male | 3(37.5%) | 8(50%) | 11(43.75%) | |
| Female | 5(62.5%) | 8(50%) | 13(56.25%) | |
| **Primary tumour location** | | | | 1 |
| Colon | 3(37.5%) | 6(37.5%) | 9(37.5%) | |
| Rectum | 5(62.5%) | 10 (62.5%) | 15(62.5%) | |
| **T of TNM** | | | | 0.5754 |
| T1 | 1(12.5%) | 2(12.5%) | 3(12.5%) | |
| T2 | 0 | 2(12.5%) | 2(6.25%) | |
| T3 | 7(87.5%) | 12 (75%) | 19 (81.25%) | |
| T4 | 0 | 0 | 0 | |
| **N of TNM** | | | | 0.0627 |
| NO | 4(50%) | 9(56.25%) | 13(53.125%) | |
| N1 | 0 | 5(31.25%) | 5(15.625%) | |
| N2 | 4(50%) | 2(12.5%) | 6(31.25%) | |
| **TNM stage** | | | | 1 |
| 0-II | 4(50%) | 9(56.25%) | 13 (43.75%) | |
| III | 4(50%) | 7 (43.75 %) | 11(56.25%) | |
| **Tumour differentian** | | | | 0.8485 |
| Well | 2(25%) | 5(33.33%) | 7 (29.165 %) | |
| Moderate | 5(62.5%) | 9(60%) | 14(61.25%) | |
| Poorly | 1(12.5%) | 1(6.67%) | 2(9.585%) | |
| **Histological type** | | | | 1 |
| Adenocarcinoma | 7(87.5%) | 15(93.75%) | 22(90.625%) | |

| | | | | |
|---|---|---|---|---|
| Mucinous adenocarcinoma | 1(12.5%) | 1(6.25%) | 2(9.375%) | |
| **Lymphatic invasion** | | | | 1 |
| Yes | 2(25%) | 4(25%) | 6(25%) | |
| No | 6(75%) | 12 (75%) | 18(75%) | |
| **Vascular invasion** | | | | 1 |
| Yes | 1(12.5%) | 3(18.75%) | 5(15.625%) | |
| No | 7(87.5%) | 13(81.25%) | 19 (84.375 %) | |
| **Perineural invasion** | | | | 0.6311 |
| Yes | 1(12.5%) | 4(25%) | 5(18.75%) | |
| No | 7(87.5%) | 12(75%) | 19 (81.75 %) | |
| **CEA before surgery** | | | | 1 |
| 55 ng/ml | 7(87.5%) | 14(87.5%) | 21(87.5%) | |
| > 5 ng/ml | 1(12.5%) | 2(12.5%) | 3(12.5%) | |
| CA19.9 before surgery | | | | 0.3333 |
| S UI/ml | 7(87.5%) | 16(100%) | 23(93.75%) | |
| > 37 UI/ml | 1(12.5%) | 0 | 1(6.25%) | |
| **Neoadjuvant treatment** | | | | 0.3521 |
| Yes | 7(87.5%) | 10 (62.5%) | 17(75%) | |
| No | 1(12.5%) | 6(37.5%) | 7(25%) | |
| **Number of chemotherapy lines** | | | | 0.5808 |
| 0-1 | 4(50%) | 11(68.75%) | 15(59.375%) | |

Table 1: Patients Characteristics for non-metastatic patients

| **Metastatic Group** | | | | |
|---|---|---|---|---|
| **Characteristics** | **Patients < 40 years (N=23)** | **Patients > 40 years (N=46)** | **Total (N=69)** | **P** |
| **Average age**<br>**Gender** | 34.69 (SD= 4.74) | 59.74 (SD=9.8) | | <0.001<br>0.3 |
| Male | 12 (52.17 %) | 18 (39.13%) | 30 (45.65% | |
| Female | 11 (47.83 %) | 28 (60.87 € %) | 39 (54.35%) | |
| Neoadjuvant treatment | | | | 0.3 |
| Yes | 12 (52.17 %) | 18 (39.13 € %) | 30 (45.65%) | |
| No | 11 (47.83 %) | 28 (60.87° | 39 (54.35%) | |
| **Number of chemotherapy lines** | | | | 0.873 |
| 0-1 | 4 (17.39 %) | 7 (15.22% | 11 (16.305%) | |
| 2 | 4 (17.39 %) | 11 (23.91%) | 15 (20.65%) | |
| > 2 | 15 (65.22 %) | 28 (60.87%) | 43 (63.045 ° | |
| **Targeted therapy** | | | | 0.71 |
| Yes | 17 (73.91 %) | 32 (69.57%) | 49 (71.74%) | |
| No | 6 (26.09 %) | 14 (30.43%) | 20 (28.26 %) | |
| **Family history** | | | | 0.1078 |
| Yes | 2 (8.7 %) | 0 | 2 (4.35 %) | |
| No | 21 (91.3 %) | 46 (100 %) | 66 (95.65 %) | |
| **KRAS mutation** | | | | 1 |

| | | | | |
|---|---|---|---|---|
| Yes | 6 (26.09 %) | 12 (26.67 %) | 18 (26.38 %) | |
| No | 17 (73.91 %) | 33 (73.33 %) | 50 (72.62 %) | |
| **NRAS mutation** | | | | 1 |
| Yes | 0 | 0 | 0 | |
| No | 22 (100 %) | 45 (100 %) | 67 (100%) | |
| **BRAF mutation** | | | | 0.3212 |
| Yes | 3 (9.52 %) | 2 (4.44 %) | 5 (6.98%) | |
| No | 19 (90.48 %) | 43 (95.56 %) | 62 (93.02% | |
| **Microsatellite instability** | | | | 0.2157 |
| MSS | 19 (82.61 %) | 42 (93.33 %) | 61 (87.97 %) | |
| MSI | 4 (17.39 %) | 3 (6.67 %) | 7 (12.03 %) | |
| **Duration of symptoms before diagnosis** | | | | 0.3457 |
| 1< month | 7 (38.89 %) | 18 (45%) | 25 (41.945%) | |
| 1-3 month | 5 (27.78 %) | 9 (22.5%) | 14 (25.14%) | |
| > 3 months | 6 (33.33%) | 8 (20%) | 14 (26.665%) | |

Table 2: Patients Characteristics for metastatic patients

Briefly, as expected, for patients in the non-metastatic and in the metastatic group, the average onset-age in EOCRC patients was significantly lower, respectively, 34.75 (SD± 3.12) vs 63.86 (SD± 7.56) years (p<0.001) and 34.69 (SD± 4.74) vs 59.74 (SD± 9.8) years (p<0.001). In the non-metastatic group, only patients >40 years were diagnosed after routine screening colonoscopy (62.5% vs 0%, p=0.0064). Young patients were always diagnosed after a certain period (1-3 months in 66.67% of cases) presenting with gastrointestinal symptoms, such as rectal bleeding (87.5%) and constipation (50%). Furthermore, in the two age groups of non-metastatic patients, there was no patient with a family history of CRC and all patients had microsatellite stable tumours.

Similarly, in the metastatic group, none of the young patient underwent screening colonoscopy (19.57% vs 0%, p=0.0243) and only 8.7% of mEOCRC patients had a family history of CRC, whereas no patient aged >40 years reported these findings.

Moreover, mEOCRC patients presented more frequently with weight loss (38.1% vs 4.65%, p=0.0013) and constipation (42.86% vs 18.6%, p=0.04) than their older counterparts (Tables 3s). Symptoms of non-metastatic and metastatic groups are reported, respectively, in Table 2s and Table 3s (supplementary material). In summary, there is no significant difference in patient's symptoms between EOCRC and older patients in the non-metastatic group (Tables 2s).

## Age impact on outcome (DFS & OS)

### Global study population

We analysed the entire population (metastatic and non-metastatic group), we observed that EOCRC patients had a similar OS compared with older patients (HR=1.398, P=0.135) (Figure 2). Median OS was 46.6 months in the EOCRC group and 66.4 months in the older group. The 5- and 10-year OS were 45.38% and 32.27% in the young population, respectively, and 59.53% and 35.03% in the older population. Moreover, EOCRC patients had a similar DFS compared with older patients (HR=0.813, P=0.2142) (Figure 2B). Median DFS was 16.3 months in the EOCRC group and 13.1 months in the older group. In the young population, the 1- and 2-year DFS were 61.29% and 27.52%, respectively. In the older population, we observed 57.2% and 34.36%, respectively.

### Non-metastatic patients

Twenty-four non-metastatic patients were included in the study. Eight patients were in the group of EOCRC and 16 in the group older than 40 years.

The majority of tumours diagnosed in non-metastatic patients were located in the rectum (62.5%). Most patients presented with moderately differentiated tumours (61.25%), being locally invasive (pT3-4 tumours) in 87.5% of cases. All non-metastatic EOCRC patients with positive lymph nodes at pathology (50%) were classified as pN2. Mucinous tumours were rare in

the two age groups (9.375%). Lymphatic, vascular and perineural invasion were exceptional in non-metastatic patients (present in 25%, 15.625% and 18.75% of cases, respectively). Tumour markers were normal in most cases (CEA ≤ 5 ng/ml in 87.5%; CA19.9 ≤ 37 UI/ml in 93.75%).

Two patients experienced recurrence and deceased during the study. Concerning overall survival, EOCRC patients had a worse outcome than older patients (HR=2, P=0.007), but only depending on two single events. No data was available for median OS, as only one patient in each group has deceased. Similarly, for DFS, EOCRC patients had shorter DFS than older patients (HR=1.75, P=0.0322), but only depending on two single events. No data was available for median OS, as only one patient in each group had recurrence.

### Metastatic patients

Sixty-nine metastatic patients were included in the study, counting 23 in the EOCRC group.

Most tumours in metastatic patients were located in the colon (58.695%). The peritoneum and liver were the two major sites of metastases (48.91% and 42.39%, respectively). Synchronous metastases were diagnosed more frequently than metachronous metastases (69.57% vs 30.43%). Tumour markers were normal in most cases (CEA ≤ 5 ng/ml in 54.35%; CA19.9 ≤ 37 UI/ml in 85.87%). Most patients presented with moderately differentiated tumours (52.175%). Advanced stage disease was diagnosed in most cases (TNM stage IV in 69.57%). Mucinous tumours were rare in the two age groups (21.74% in mEOCRC patients vs 6.52% in older patients, p=0.1062). Lymphatic (70% in mEOCRC patients vs 62.5 in older patients, p=0.66), vascular (70% in mEOCRC patients vs 55% in older patients, p=0.266) and perineural invasion (50% in mEOCRC patients vs 52.5% in older patients, p=0.87, respectively) were common in metastatic patients, regardless of the age of the patients. Younger patients were more likely to get neoadjuvant treatment than their older counterparts. However, the difference is not statistically significant (52.17% vs 39.13%, p=0.3). No significant difference in MSI status was observed between the two age groups.

In the younger population, 5- and 10-year OS were 35.15% and 14.06%, respectively, as in the older population, they were 47.65% and 21.99%, respectively. OS tended to be increased in the older group, with a median survival of 58.3 months compared to 42.8 months in EOCRC patients, but this difference did not reach statistical significance (p=0.1618) (Figure 3A).

In the younger group, 1- and 2-year DFS were 51.51% and 10.7%, respectively, as in the older group, they were 40.99% and 15.94%, respectively. DFS tended to be increased in the younger group having a median survival of 13.4 months compared to 10.7 months for patients in the older group (HR=0.756), but this difference did not reach statistical significance (p=0.2335) (Figure 3B).

## Supplementary Data

| Metastatic patients | Non-metastatic patients |
|---|---|
| Primary tumour location (colon or rectum) | Primary tumour location (colon or rectum) |
| CEA before surgery (or >5) | TNM |
| CA19.9 before surgery (37 or> 37) | T (0-4) |
| Metastatic site | N (0-2) |
| Liver | TNM stage (I-III) |
| Peritoneum | Tumour differentiation (well, moderate, poorly) |
| Liver & peritoneum | Histological type (adenocarcinoma, mucinous) |
| Synchronous metastasis | Lymphatic invasion |
| Metachronous metastasis | Vascular invasion |
| If PM | Perineural invasion |
| PCI score (≤7 or > 7) | CEA before surgery (≤5 or >5) |
| If LM<br>Maximal size at diagnosis (≤ 25 or > 25)<br>Number at diagnosis ((≤ 4 or > 4) | CA19.9 before surgery (≤37 or >37) |

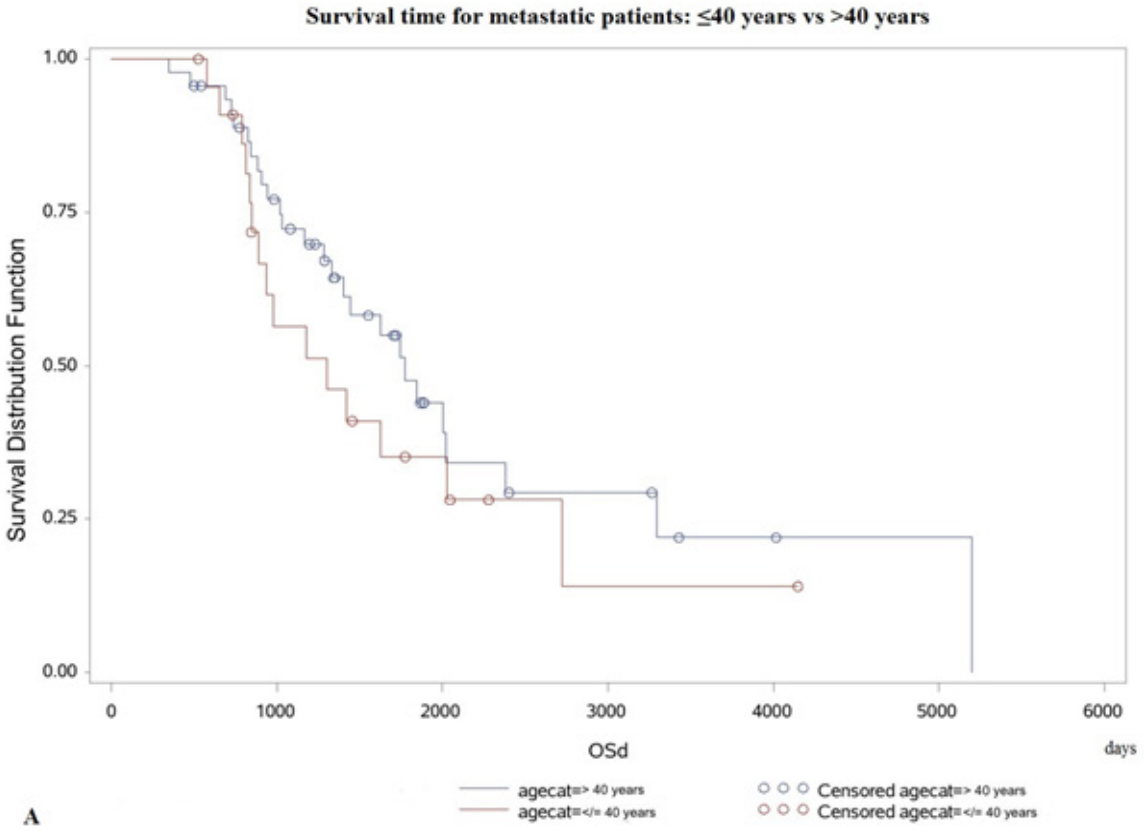
Table 1s: Matching factors for metastatic and non-metastatic patients
For primary tumour location, we consider the following as "right colon": caecum and right colon": transverse colon, left colon and sigmoid and "rectum": recto-sigmoid junction, rectum.

| Non-metastatic groups | | | | |
|---|---|---|---|---|
| **Symptoms** | **Patients s 40 years** (N=8) | **Patients > 40 years** (N=16) | **Total** (N=24) | **P** |
| **Abdominal pain** | | | | 1 |
| Yes | 3 (37.5 %) | 5 (31.25 %) | 8 (34.375%) | |
| No | 5 (62.5 %) | 11 (68.75 %) | 16 (65.625%) | |
| **Rectal bleeding** | | | | 0.1893 |
| Yes | 7 (87.5 %) | 9 (56.25 %) | 16 (71.875%) | |
| No | 1 (12.5 %) | 7 (43.75 %) | 8 (28.125%) | |
| **Weight loss** | | | | 1 |
| Yes | 1 (12.5 %) | 1 (6.25 %) | 2 (9.375 %) | |
| No | 7 (87. %) | 15 (93.75 %) | 22 (90.625 %) | |
| **Occlusion** | | | | 1 |
| Yes | 0 | 1 (6.25 %) | 1 (3.125%) | |
| No | 8 (100 %) | 15 (93.75 %) | 13(96.875%) | |
| **Constipation** | | | | 0.3625 |
| Yes | 4 (50 %) | 4 (25 %) | 8 (37.5 %) | |
| No | 4 (50 %) | 12 (75 %) | 16 (62.5%) | |
| **Diarrhoea** | | | | 0.5362 |
| Yes | 0 | 2 (12.5 %) | 2 (6.25%) | |
| No | 8 (100 %) | 14 (87.5 %) | 22 (93.75 %) | |
| **Peritonitis or bowel perforation** | | | | 1 |
| Yes | 0 | 0 | 0 | |
| No | 8 (100 %) | 16 (100 %) | 24 (100 %) | |
| **Melena** | | | | 0.6311 |
| Yes | 1 (12.5 %) | 4 (25 %) | 5 (18.75 %) | |
| No | 7 (87.5 %) | 12 (75 %) | 19 (81.25 %) | |
| **Change in bowel habits** | | | | 1 |
| Yes | 2 (25 %) | 4 (25 %) | 6 (25%) | |
| No | 6 (75%) | 12 (75 %) | 18 (75%) | |
| **Iron deficiency anaemia** | | | | 0.6311 |
| Yes | 1 (12.5 %) | 4 (25 %) | 5 (18.75%) | |
| No | 7 (87.5 %) | 12 (75 %) | 19 (81.25 %) | |
| **Weakness, fatigue** | | | | 1 |
| Yes | 1 (12.5 %) | 1 (6.25 %) | 2 (9.375%) | |
| No | 7 (87.5 %) | 15 (93.75 %) | 22(90.625% | |
| **Rectal pain** | | | | 1 |

Table 2s: Symptoms in non-metastatic patients

| Metastatic groups | | | | |
|---|---|---|---|---|
| Symptoms | Patients s 40 years (N= 23) | Patients > 40 years (N=46) | Total (N=69) | P |
| **Abdominal pain** | | | | 0.07 |
| Yes | 17 (80.95 %) | 25 (58.14%) | 42 (69.545%) | |
| No | 4 (19.05 %) | 18 (41.86 %) | 22 (30.455%) | |
| **Rectal bleeding** | | | | 0.41 |
| Yes | 8 (38.1 %) | 12 (27.91 %) | 20 (31.25%) | |
| No | 13 (61.9 %) | 31 (72.09 %) | 49 (68.25%) | |
| Weight loss | | | | 0.0013 |
| Yes | 8 (38.1 %) | 2 (4.65 %) | 10 (15.63%) | |
| No | 13 (61.9 %) | 41 (95.35 %) | 54 (84.38%) | |
| Occlusion | | | | 0.39 |
| Yes | 7 (33.33 %) | 10 (23.26 %) | 17 (26.56%) | |
| No | 14 (66.67 %) | 33 (76.74 %) | 47 (73.44%) | |
| Constipation | | | | 0.04 |
| Yes | 9 (42.86 %) | 8 (18.6 | 17 (26.56 %) | |
| No | 12 (57.1 14 %) | 35 (81.4%) | (73.44%) | |
| Diarrhoea | | | | 0.4215 |
| Yes | 4 (19.05 %) | 4 (9.3%) | 8 (12.5%) | |
| No | 17 (80.95 %) | 39 (90.7%) | 56 (87.5%) | |
| **Peritonitis or bowel perforation** | | | | 0.4762 |
| Yes | 2 (9.52 %) | 8 (18.6) %) | 10 (15.63%) | |
| No | 19 (90.48 %) | 35 (81.4 %) | 54 (84.38 %) | |
| **Melena** | | | | 0.1042 |
| Yes | 2 (9.52 %) | 0 | 2 (3.13%) | |
| No | 19 (90.48 %) | 43 (100 %) | 62 (96.88 %) | |
| **Change in bowel habits** | | | | 0.54 |
| Yes | 11 (52.38 %) | 19 (44.19% | (46.88% | |
| No | 10 (47.62 %) | 24 (55.81%) | (53.13%) | |
| **Iron deficiency anaemia** | | | | 0.4215 |
| Yes | 4 (19.05 %) | 4 (9.3 ° %) | 8 (12.5%) | |
| No | 17 (80.95 %) | 39 (90.7 %) | 56 (87.5%) | |
| **Weakness, fatigue** | | | | 1 |
| Yes | 2 (9.52 %) | 5 (11.63 %) | 7 (10.94%) | |
| No | 19 (90.48 %) | 38 (88.37%) | 57 (89.06%) | |
| **Rectal pain** | | | | 0.3202 |

**Table 3s:** Symptoms in metastatic patients



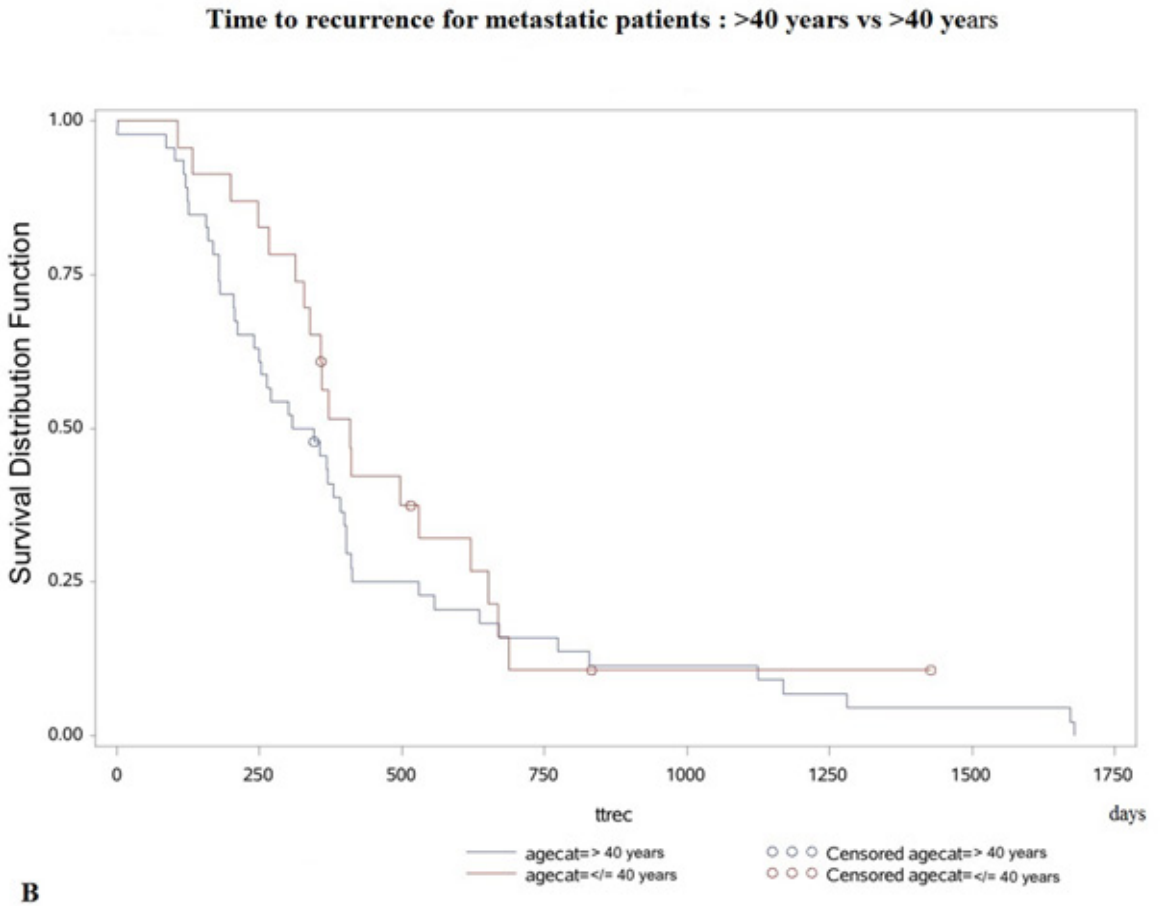
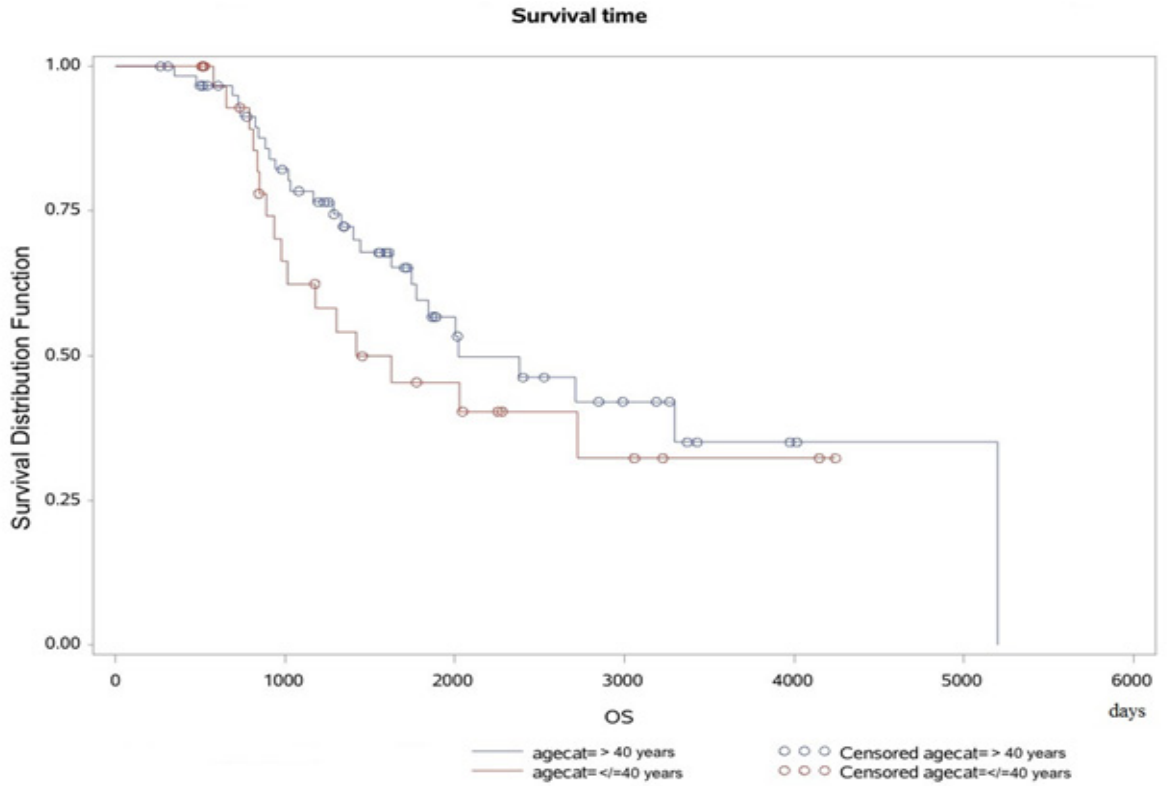
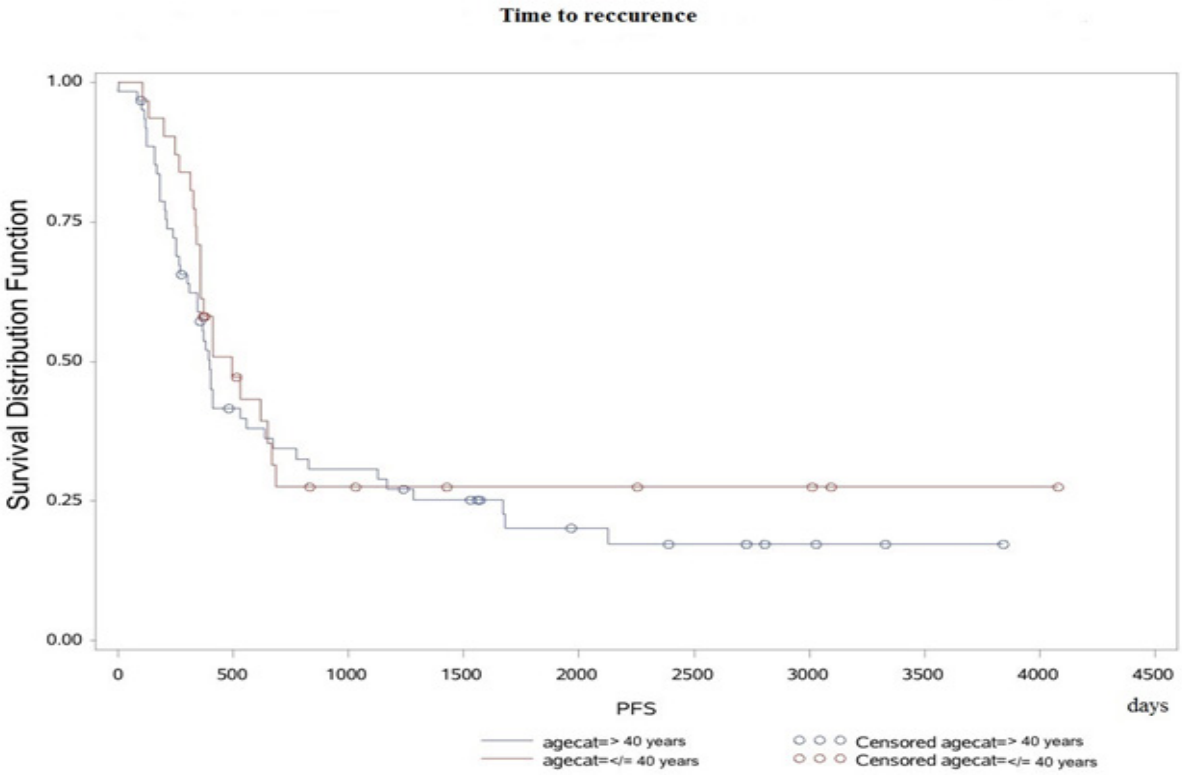




Figure 2: Outcomes ((a) OS and (b) PFS) in function of age for the global population




A




B

Figure 3: Outcomes ((a) OS and (b) PFS) in function of age for the CRC metastatic group

## Discussion

The results of our study showed that the outcome in terms of overall survival and disease-free survival are similar in EOCRC and patients older than 40 years when they are matched for major prognostic factors. The general feeling that younger patients have a worse prognosis could be related to the fact that their CRC is diagnosed at a more advanced stage as none of these EOCRC are diagnosed at screening colonoscopy, conversely to older patients (62.5% vs 0%, p=0.0064).

The incidence and mortality rates of CRC have evolved constantly over the past two decades, yet not all parts of the world share the same transition. Arnold et al. identified distinct coexisting patterns in CRC incidence and mortality across the globe, appearing highly dependent on countries' development levels. Consequently, a high human development index (HDI) was associated with stabilizing or even decreasing incidence and mortality rates [12]. This decline was primarily objectified in individuals aged over 50 and has been described by several studies. Reasons for these observations seem to be firmly related to screening and prevention programs, early intervention as well as better practices in cancer treatment and management [4,7,12,13].

An opposite tendency has been reported for individuals below the average screening age [14]. Several studies agreed that in many high-income countries, incidence rates in adults below 50 years have been increasing since the mid-1990s. In Europe, a rise from 1.6-9.3% in colon and 0-3.5% in rectal cancer in subjects aged 20-39 from 1990-2016 was stated by Vuik, *et al.* [7]. Likewise, in the United States between 2012-2016, Siegel et al. noted an annual rise of 2.2% in patients younger than 50 years [4]. Saad et al. conducted a systemic review of studies worldwide, examining population-level trends in EOCRC. There was substantial variability in reporting, but they could provide empirical evidence confirming the increasing incidence of EOCRC (pooled overall APC of + 1.33%; $p < 0.0001$) [15].

One study offered insight into future projections. Bailey et al. predicted that by 2030, 10% of all colon and 22% of all rectal cancers are expected to be diagnosed in adults younger than 50 years. These predictions seem pretty challenging compared to observations made in 2010 (4.8% and 9.5% for colon and rectal cancer, respectively) [16]. All latter studies express concern about this evolving trend, believed to become a major public health issue in the future.

There is an inconsistency between individual studies in defining EOCRC. No actual cut-off age has yet been determined, and it remains a subject of controversy in the literature. Most studies considered young CRC patients as those diagnosed before the average screening age (<50 years) [4,16-18]. Conversely, there is an extensive range of publications using arbitrary predefined age cut-offs with extreme variability [15, 19-21]. In the present study, we chose the cut-off age of 40 years for defining EOCRC patients, following the NCIs' description of adolescents and young adults (AYA) defined by the age range of 15–39 years [22]. In addition, several extensive studies used this cut-off age [23]. Importantly, current age-group subdivision remains a limitation for interpreting and comparing studies addressing EOCRC.

The most unequivocal finding in our study was that none of the young patients had routine screening colonoscopy. Diagnosis of CRC was in 100% of cases preceded by a relative period of diverse symptoms. These findings were predictable because the average onset-age for screening in Belgium is recommended for adults >50, except for patients with a family history or known predisposing syndrome [13]. In their study, Kim et al. reported that 80.5% of young patients presented with symptoms before diagnosis, rectal bleeding being the most frequently seen symptom. Intervals between symptom onset and diagnosis were around 1.7 months [20]. Another study showed that 84% of young adults had symptoms including rectal bleeding (76.5%), abdominal pain (58%), and altered bowel habits (71%). 21% had symptoms for >6 months before diagnosis [24]. In our study, non-metastatic patients were most commonly diagnosed with rectal cancer (62.5%). Frequent symptoms for these patients were mainly rectal bleeding (87,5%) and constipation (50%). Furthermore, most symptoms persisted for 1-3 months (66.67%) before CRC was diagnosed. Metastatic patients were diagnosed with colon cancer more frequently (52.17% vs 47.83% rectal cancer). Abdominal pain (80.95%) and changes in bowel habits (52.38%) were the most prevalent symptoms, and their duration variated equally between <1 month to >3 months.

OS and DFS of the total study population were not significantly different between young and older patients. Median OS was 46.6 months in the EOCRC group and 66.4 months in the older group ($p>0.05$). Several studies shared these outcomes (8) (23), others reported a better survival in the young [17]. Wang et al. compared three different age groups (20–40, 41–50, and >50 years) of CRC patients. They concluded that young patients had a significantly better cancer-specific survival rate than patients >50 years. They described the same tendency after stratifying by each stage in different age groups [21]. Most studies compared

two age groups, broadly defined by distinct cut-off ages, without considering different prognostic factors for survival. The results mostly pointed out that young patients had less favourable survival compared to older counterparts. Reasons for these findings were primarily delayed diagnosis (low suspicion for cancer in this age group, unspecific symptoms misleading diagnosis) and more advanced stage disease at diagnosis in EOCRC patients. These patients were generally compared to the average CRC population with fewer advanced cases at diagnosis [4]. Some other studies calculated stage specific survival rates in the two populations. There are different outcomes for each study [13,19].

Outcomes related to adjuvant chemotherapy in function of patient's age is also a matter of debate. Two studies stated that EOCRC patients were more likely to receive adjuvant chemotherapy at all stages compared to older patients [25,26]. This attitude noted no apparent survival gain. Berian et al. pointed out that young patients often got overtreated (multi-agent regimens) with minimal improvement in survival. Our study did not observe a significant difference between the number of chemotherapy lines used in both age groups. However, a more considerable number of chemotherapy regimens indicated worse outcomes.

In the general CRC population, hereditary cancer syndromes represent 2% to 5% of all cases [27]. The proportion of these syndromes vary within different age groups. In adults <40 years, the proportion rises to almost 23% [4,28]. Mork et al. studied a population of CRC patients younger than 35 years at the time of diagnosis, and up to 1/3 of their study population presented with hereditary syndromes [29]. A prospective study of 450 patients diagnosed with CRC before the age of 50 showed that 16% were linked to genetic syndromes, among which 8% account for Lynch syndrome (MSI high tumours). Surprisingly, most patients affected by these conditions did not report any cancer family history [30]. Our findings confirm these observations. We identified a proportion of 8% of patients with MSI high status (suggestive for Lynch syndrome), although only 2.15% of patients presented with a family history of CRC, all observed in the EOCRC group. Out of vigilance, Pearlman, *et al.* suggest furthermore genetic counselling and testing with a multigene panel (for wide spectrum mutations) for all patients with early-onset CRC. However, most EOCRC cases remain sporadic and do not coincide with any predisposing syndromes [13]. Interestingly, cases of our study presenting with family history were associated with a decreased OS and DFS ($p \leq 0.0001$). These findings are, however, inappropriate for interpretation because of their minor frequency. MSI high tumours, not dependant on age groups, showed a better OS than MSS tumours ($p=0.0409$). These findings were consistent with those found in the literature [18,31].

Limitations of this study were the small sample size of the young group, single specialised institution bias and the retrospective design of the study. Moreover, this analysis concerned a specific targeted population (matched) and global results on the older population should be interpreted in this context. We chose to include only patients that underwent curative-intent surgery, which downsized our cohort. No data on cancer-specific survival was available. The strength of this study is the choice of 40years as a cut-off for defining young patients.

In conclusion, the process of matching patients based on significant, well established, risk factors for survival allowed the identification and comparison of patients with a similar pathology. The consideration of several predictive factors for survival allowed to focus mainly on age as a marker for survival. We did not find significant differences between survival in both age groups. In this study, age is not considered being an independent risk factor for survival. Young metastatic patients presented more often with weight loss and constipation than older patients. We found no difference in genetics and mutations between the two age groups.

## Conflict of interest:

Authors have no conflict of interest to declare.

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