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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Older patient • Over-80 • Clinical trial • Colorectal cancer • Eligibility • Inclusion

Abstract

Background. The primary objective was to evaluate the rates of older patients with colorectal cancer (CRC) who were eligible for a clinical trial, invited to participate, and, ultimately, included. The secondary objective was to assess the reasons for ineligibility, noninvitation, and noninclusion and factors associated.

Materials and Methods. The Sujets AGés dans les Essais Cliniques (SAGE; Older Subjects in Clinical Trials) multicenter prospective cohort was established in seven centers (10 departments of medical oncology, digestive oncology, and digestive surgery) between 2012 and 2016. All patients with CRC aged 65 or older were studied. The endpoints were clinical trial availability, patient's eligibility, invitation, and enrollment in a trial.

Results. We included 577 older patients (mean age ± SD: 75.6 ± 7 years; males: 56%; metastasis: 41%). Thirty-seven trials were ongoing (one trial for older patients). Of the 474 patients with at least one available trial for their cancer stage and site, 127 (27%) were eligible; 84 of these 127 (66%) were invited to participate, and 70 of these 84 (83%) were included. In a multivariate analysis, noninvitation was found to be associated with older age (p = .016): adjusted relative risk (95% confidence interval), 0.14 (0.02–0.60) for ≥80 vs. 65–69; 0.54 (0.18-1.04) for 75–79 vs. 65–69; 0.47 (0.17-0.93) for 70–74 vs. 65–69.

Conclusion. Three-quarters of older patients with CRC were ineligible for a clinical trial. One-third of the eligible patients were not invited to participate in a trial, and 17% of invited patients were not included. Few trials are reserved for older patients. Patients aged 80 or older were significantly less likely to be eligible for a trial and invited to participate. *Clinical trial identification number*: NCT01754636. ***The Oncologist*** 2019;24:e1351–e1359

Implications for Practice: The results of this study suggest that barriers to participation of older patients in clinical trials are particularly marked at age 80 years or older. Secondly, the results emphasize the need for trials for older patients. Thirdly, there is also a need for more pragmatic "real-world" trials, rather than solely randomized trials performed in idealized settings with strictly selected patients. Large prospective observational cohorts with a precise follow-up of toxicity, functional decline, and quality of life may constitute one way of generating more data on the risk-benefit ratio for cancer treatments in older patients.

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Introduction

Sixty percent of new cases of cancer occur in people aged 65 or older, and 30% occur in people aged 75 or older. However, older patients are underrepresented in clinical trials: less than 25% of U.S. cancer trial participants are aged 65 or older, and less than 10% are aged 75 or older [1]. Although disparities with regard to the sex ratio, race, and the pediatric age group have decreased among cancer trial populations in the last 20 years, there has been little change with regard to older age [2–6].

The underrepresentation of older patients in cancer trials reduces our knowledge of the benefit-risk balance of cancer treatments in this population and restricts older patients' access to innovative therapies. Indeed, in "real-life" studies, older patients are less likely to receive chemotherapy [7, 8].

Many studies have addressed the lack of enrollment of older patients with cancer in clinical trials. However, most of these studies were based on trial registers or systematic reviews and focused on analyses of the trials' eligibility criteria [9–11]. Few studies have investigated the entire inclusion pathway (i.e., availability of a trial, eligibility criteria, invitation to participate, and inclusion) and the barriers encountered at each step in this pathway [12].

Colorectal cancer (CRC) is one of the more frequent cancers among older patients, affecting both older men and women, and two-thirds of deaths from CRC occur in older patients. Moreover, ongoing clinical trials focused on CRC are numerous. Therefore, CRC was a good condition to investigate the issue of underrepresentation of older patients in clinical trials.

To the best of our knowledge, there were no data regarding participation of older patients with CRC in clinical trials. Nevertheless, a recent study including >200,00 patients with CRC with >50% of patients 70 years or more showed that patients treated in hospital with high rates of research participation had lower postoperative mortality and increased 5-year survival [13].

The primary objective was to evaluate the rates of older patients with colorectal cancer who had an available trial, who were eligible, invited to participate in trials, and ultimately included. The secondary objective was to assess the reasons for trial ineligibility, noninvitation, and noninclusion, and to identify any associated factors.

Materials and Methods

The SAGE prospective, observational, multicenter cohort study was conducted from January 2012 to November 2015 in 10 departments in four cities in the Greater Paris area, France. Patients' verbal consent was obtained in accordance with French Law for noninterventional studies. The protocol was approved by the appropriate ethics committee (CPP Ile-de-France IV, Paris, France). The SAGE cohort study was registered at ClinicalTrials.gov (NCT01754636). The study reporting complied with the STROBE guidelines for observational studies [14].

Clinical Trials Studied

All trials dealing with CRC (i.e., therapeutic, diagnostic, and monitoring aspects) and that were recruiting in any of the investigating centers during the study period were taken into account.

Population Studied

All consecutive patients with CRC aged 65 or older and who had been treated in one investigating centers during the study period were considered.

Endpoints

For each patient, we prospectively recorded (a) the availability of a trial, (b) eligibility for at least one trial, (c) invitation by a physician to participate, and (d) inclusion. A trial was considered to be available if, at the time of the treatment decision for a given patient in the study center, (a) the trial was recruiting and (b) the trial's inclusion criteria corresponded to patient's tumor site (the colon, rectum, or both) and stage (localized or metastatic). A patient was considered to be eligible for a trial if he/she met all the inclusion criteria and none of the noninclusion criteria. A patient was considered to have been invited to participate in a clinical trial if his/her participation had been requested by a trial investigator. For each eligible patient, the clinical research assistant directly asked the physician if he/she offered trial participation and the reason(s) if not offering.

Covariates

On inclusion in the present study, the patients' sociodemographic, oncologic, geriatric, and other characteristics of were recorded on a standardized electronic case-report form (CleanWeb; Telemedicine Technologies SAS, Boulogne-Billancourt, France). The characteristics of the trials at each center (type of sponsor, trial phase, type of investigational treatment, etc.) were also recorded in detail. Data on the reasons for noninvitation and noninclusion were recorded via a list of closed (yes/no) questions answered by the physician and the patient, respectively (supplemental online Tables 1 and 2). Geriatric assessment variables collected were Mini-Mental Status Examination, history of dementia, activity of daily living score, Timed Up and Go test, mini-Geriatric Depression Scale, polymedication, incontinence, and Mini-Nutritional Assessment test.

Sample Size

We postulated an inclusion rate of 10%. Based on an accuracy of 3%, an α risk of 2.5%, and 10% of patients with data nonavailable, 553 patients were needed.

Statistical Analysis

Endpoints were expressed as the rates (%) with 95% confidence intervals (CI). Four age classes were considered: 65–69, 70–74, 75–79, and ≥80. The baseline characteristics of the patients in each age class were compared using chi-squared or Fischer and Kruskal-Wallis tests, and pairwise comparisons were performed using the Sidak's method. The characteristics of patients invited to participate in trials and those not invited to participate were compared. Factors associated with an invitation to participate were analyzed in univariate and multivariate logistic regression analyses and quantified first as crude and adjusted odds ratios and then as relative risks (RRs) and 95% CI [15]. Variables with $p < .20$ in a univariate analysis were considered for a multivariate

analysis. Manual stepwise procedure was done to identify confounders and variables independently associated with invitation. Only variables significantly associated with invitation were kept in the final multivariate model. Hierarchical models (with the patient at level 1 and the center at level 2) were considered. The discriminative properties of the final multivariate model were assessed. The threshold for statistical significance was set to $p < .05$. Statistical analyses were performed with Stata software (version 12.0; StataCorp. 2011, College Station, TX), and R software (version 1.0.136; R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of Trials and Patients

Between 2012 and 2015, a total of 37 trials were ongoing in at least one of the participating centers. The trials' characteristics are detailed in supplemental online Table 3. Five trials had an upper age limit (70 or 75 years). One trial was specifically for older patients aged 75 or older (PRODIGE 20). It was a randomized noncomparative phase II trial evaluating bevacizumab combined with chemotherapy versus chemotherapy alone in patients with metastatic CRC aged 75 or older. The main endpoint was a cocriterion based on tumor control and quality of life [16]. In total, 577 consecutive patients with CRC aged 65 or older were included (mean age ± SD: 75.6 ± 7 years; ≥80 years, 27%; male, 56%; Table 1). Patients aged 80 and older were more likely to have an altered performance status (PS), live alone, and have a caregiver than were patients in the three younger age classes (65–69, 70–74, and 75–79; Table 1). The patients aged 80 and older also had a lower educational level and more comorbidities than patients in the 65–69 age group (Table 1). From the 416 patients aged 70 or older, 75 had a geriatric assessment. Parameters of geriatric assessment are detailed in Table 1.

Trial Availability, Eligibility, Invitation, and Inclusion Rates for Older Patients

Figure 1 displays the patient attrition at each step: in the first step, 474 patients (82%) had an available trial; at the second step, 127 (27%) were eligible for a trial; at the third step, 84 (66%) were invited to participate in a trial; and at the fourth step, 70 (83%) were included. Four ineligible patients were erroneously invited to participate in a trial, and one of these was included in a trial. Overall, 70 patients (12%; 95% CI, 10–15) were included in a trial.

From the 14 patients for whom the PRODIGE 20 was available, 5 (36%) were eligible; 3 of these (60%) were invited, and 3 (100%) were included.

Trial Availability, Eligibility, Invitation, and Inclusion Rates by Age Class

The trial availability, eligibility, invitation, and inclusion rates are shown by age class in Figure 2. There was a significant overall difference in eligibility between the four age classes. In fact, pairwise comparisons showed that patients in the 65–69, 70–74, and 75–79 age classes did not differ in eligibility, whereas the eligibility rate for patients aged 80 or older was significantly lower ($p < .02$ for all three pairwise comparisons). Similarly, there was a significant overall difference in invitation between the four age classes. In fact, pairwise comparisons showed that invitation rate for patients aged 80 or older was significantly lower than for patients in the 65–69 age class ($p = .02$). The inclusion rate did not differ significantly from one age class to another. Overall, 70 (12%) patients were included in a trial (30 [43%] patients aged 65–69 years; 19 [27%] aged 70–74 years; 17 [24%] aged 75–79 years; and 4 [6%] aged 80 years or older; $p < .001$).

Reasons for Ineligibility (According to the Inclusion and Noninclusion Criteria), Noninvitation, and Noninclusion

Ineligibility was most frequently related to tumor characteristics (in addition to stage and location used to defined availability of trial): presence of cerebral or bone metastasis, genomic alteration, synchronous tumor, distance of tumor to anal margin (for rectal cancer), resectability (of the tumor or hepatic metastasis), complications (occlusion, perforation), and CarcinoEmbryonic Antigen level (Fig. 1; Table 2). The second most frequent reason was the absence of an examination required for inclusion or an excessively long time interval between this examination and inclusion (more than 2 or 4 weeks, depending on the trial). The third most frequent reason was a history of anticancer treatment, concomitant treatment, or an overly short time interval since the withdrawal or cessation of these treatments. The other main reasons were (in order of decreasing frequency) altered PS (>PS1 or > PS2, depending on the trial); abnormal levels of hematologic, renal, or hepatic biomarkers; age limits (70 or 75 years); and comorbidities (Fig. 1). There were no significant differences in the frequencies of ineligibility criteria between the age classes (Table 2). However, the proportions of patients meeting the ineligibility criteria were always higher in the ≥80 group than in the other age classes: particularly for required examinations, PS, and, as expected, age limits (nonsignificant trends; $p < .10$) leading to significantly lower eligibility.

The main reason that prompted physicians not to invite patients to participate in a trial was a comorbidity or a worsened PS that, in the physician's opinion, was prejudicial to participation—even when the worsened PS was compatible with the trial's eligibility criteria. The second most frequent reason was a logistic problem in the department (e.g., the positron emission tomography scan appointment required for the trial). The third most frequent reason was the physician's opinion of the investigational treatment. The fourth most frequent reason was the physician's lack of time. When considering patients who had been invited to participate in a trial, the main reasons for refusal were fear of side effects and doubt about the treatment's efficacy, followed by the trial's follow-up procedures or the need for additional procedures (Fig. 1).

Factors Associated with Invitation to Participate in a Clinical Trial

Among patients eligible for a trial, those invited to participate in a clinical trial were younger and had stage III or IV cancer (vs. stages I or II), better PS, and a normal nutritional status (according to body mass index; BMI) relative to those not invited (Table 3). The likelihood of invitation was not

Table 1. Baseline characteristics of the SAGE study overall population and by age class

Characteristics	Overall, *n* (%)	65–69 yr, *n* (%)	70–74 yr, *n* (%)	75–79 yr, *n* (%)	≥80 yr, *n* (%)	*p* value
Number of patients	577	157 (27)	134 (23)	133 (23)	153 (27)	
Mean age (± SD)	75.6 (±7.0)	67.5 (±1.5)	72.6 (±1.5)	77.5 (±1.5)	85.02 (±3.6)	
Sex (M)	323 (56)	99 (63)	75 (56)	77 (58)	72 (47)[a,b]	.04
Living alone (*n* = 572)	177 (31)	38 (25)	36 (27)	39 (30)	64 (42)[a]	.006
Residence (*n* = 574)						.53
At home	522 (91)	148 (95)	122 (91)	118 (89)	134 (88)	
At a family member's home	34 (9)	7 (4)	7 (5)	9 (7)	11 (7)	
In long-term care	5 (1)	0	2 (1)	2 (2)	1 (1)	
In a nursing home	13 (2)	1 (1)	3 (2)	3 (2)	6 (4)	
Presence of a caregiver (*n* = 551)	338 (61)	81 (54)	81 (62)	72 (58)	104 (71)[a]	.017
Educational level (*n* = 547)						.005
Primary	157 (29)	27 (18)	36 (28)	44 (36)[c]	50 (35)[a]	
Secondary	203 (37)	57 (37)	51 (40)	40 (32)[c]	55 (38)[a]	
Higher education	187 (34)	6 (45)	41 (32)	39 (32)[c]	39 (27)[a]	
Median home-to-hospital distance (Q1–Q3), km (*n* = 695)	10 (5–20)	10 (5–25)	10 (5–20)	10 (5–20)	10 (5–18)	.38
Cancer site (colon)	431 (75)	113 (72)	99 (74)	105 (79)	114 (74)	.59
Cancer stage						.1
Stage 0 (Tis. N0. M0)	15 (3)	5 (3)	2 (2)	5 (4)	3 (2)	
Stage I (T1/T2. N0. M0)	36 (6)	8 (5)	7 (5)	10 (8)	11 (7)	
Stage II (T3/T4. N0. M0)	112 (19)	22 (14)	19 (14)	22 (16)	49 (32)	
Stage III (T1–T2/T3–T4. N1/N2. M0)	172 (30)	50 (32)	46 (34)	41 (31)	35 (23)	
Stage I–II or III unknown	6 (1)	4 (3)	1 (1)	1 (1)	0	
Stage IV (all T. all N. M1)	236 (41)	68 (43)	59 (44)	54 (40)	55 (36)	
Performance Status (*n* = 563)						<.001
0	180 (32)	62 (41)	54 (41)	33 (26)	31 (21)[a,b,d]	
1	262 (47)	72 (47)	56 (43)	70 (53)	64 (43)[a,b,d]	
2	98 (17)	18 (12)	14 (11)	25 (19)	41 (27)[a,b,d]	
3	12 (3.5)	1 (1)	5 (4)	3 (2)	12 (8)[a,b,d]	
4	2 (0.5)	0	1 (1)	0	1 (1)[a,b,d]	
Comorbidities (presence) (*n* = 576)	419 (73)	94 (60)	97 (72)	98 (74)[c]	130 (85)[a]	.001
BMI (base level: 21–24.9), kg/m^2 (*n* = 564)	202 (35.8)	54 (35.3)	45 (33.8)	47 (35.9)	56 (38.1)	.96
<21 (underweight)	129 (22.9)	34 (22.2)	29 (21.8)	33 (25.2)	33 (22.5)	
≥ 25 (overweight, obesity)	233 (41.3)	65 (42.5)	59 (44.4)	51 (38.9)	58 (39.5)	
Weight loss (*n* = 574)	336 (58.4)	103 (65.6)	72 (53.7)	75 (56.8)	86 (57.0)	.19
Frailty screening (G8 score ≤ 14 out of 17; *n* = 379 ≥ 70 y)	299 (79)	NA	86 (70)	88 (75)	125 (90)[b,d]	<.001
Geriatric assessment performed (*n* = 416)	75 (13)	NA	9 (7)	22 (17)	42 (28)[b,d]	<.001
MNA normal (≥24)	18 (51.4)	NA	2 (100)	8 (57.1)	8 (42.1)	.41
Malnutrition risk (17–23)	15 (42.9)	NA	0	6 (42.9)	9 (47.4)	
Malnutrition (<17)	2 (5.7)	NA	0	0	2 (5.7)	
Median MMSE score out of 30 (Q1–Q3) (*n* = 36)	25.5 (21–28.5)	NA	30 (30–30)	27 (24–29)	23.5 (19–28)	.08
Dementia (*n* = 35)	2 (5.7)	NA			2 (10.5)	.41
Median ADL score out of 6 (Q1–Q3) (*n* = 64)	6 (5–6)	NA	5.5 (4.5–6)	6 (5.5–6)	6 (5–6)	.4
TGUG altered >20 s (*n* = 27)	10 (37)	NA	1 (50)	2 (18.2)	7 (50)	.24
Mini-GDS altered, ≥1 (*n* = 56)	15 (26.8)	NA	1 (14.3)	4 (22.2)	10 (32.3)	.54

(continued)

Table 1. (continued)

Characteristics	Overall, *n* (%)	65–69 yr, *n* (%)	70–74 yr, *n* (%)	75–79 yr, *n* (%)	≥80 yr, *n* (%)	*p* value
Incontinence (*n* = 73)	18 (24.7)	NA	2 (22.2)	4 (18.2)	12 (28.6)	.65
Polymedication >5 drugs per d (*n* = 73)	43 (58.9)	NA	5 (55.6)	12 (54.6)	26 (61.9)	.83

Unless otherwise indicated, variables are expressed as *n* (%) otherwise indicated.
p values are from a chi-square test for qualitative variables and a Kruskal-Wallis test for quantitative variables.
[a]Significant pairwise comparisons between ≥80 yr versus 65–69 yr.
[b]Significant pairwise comparisons between ≥80 yr versus 70–75 yr.
[c]Significant pairwise comparisons between ≥75 yr versus 65–69 yr.
[d]Significant pairwise comparisons between ≥80 yr versus 75–80 yr.
Abbreviations: ADL, activity of daily living; BMI, body mass index; IADL, instrumental activity of daily living; M, male; Mindi-GDS, Mini Geriatric Depression Scale; MMSE, Mini-Mental Status Examination; MNA, Mini-Nutritional Assessment; NA, not applicable; TGUG, timed get-up-and-go.

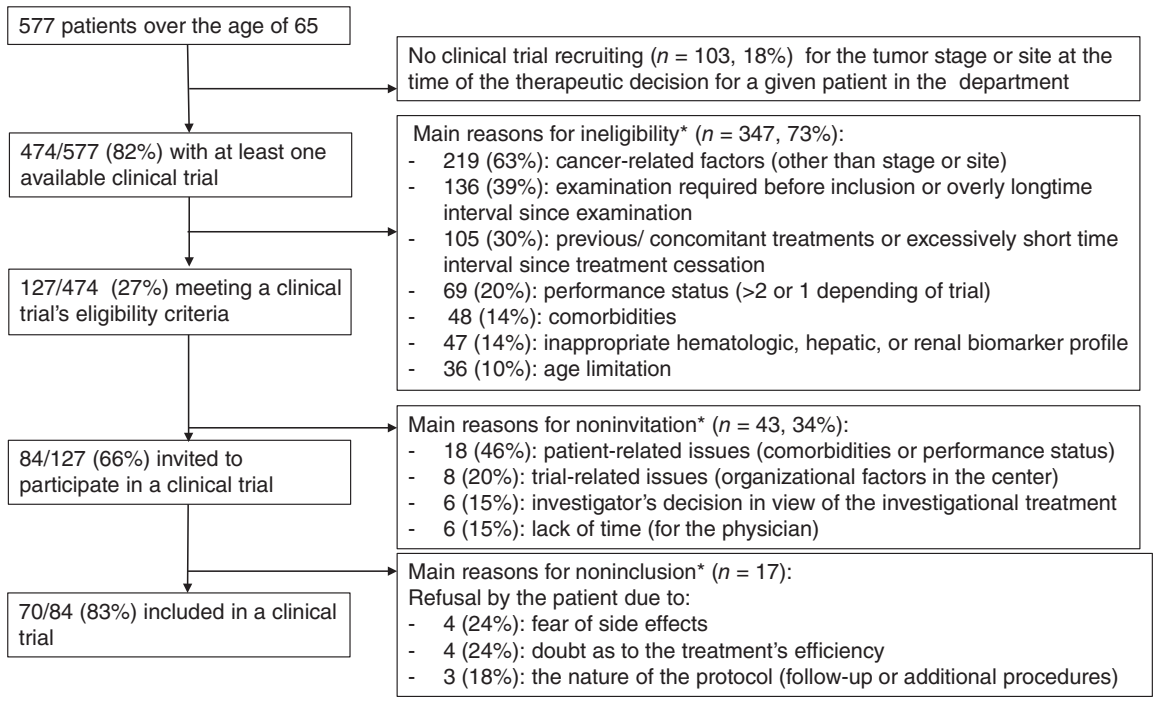

Figure 1. Study flow-chart.
*Not mutually exclusive.

associated with the cancer site (colon vs. rectum), comorbidities, sex, or sociodemographic characteristics (living alone, living at home, presence of a caregiver, educational level, home-to-hospital distance and journey time, and transportation mode).

In a multivariate analysis adjusted for PS and BMI, older age was independently associated with a lower likelihood of invitation (p = .016): adjusted RR (95% CI), 0.14 (0.02–0.60) for 80 vs. 65–69; 0.54 (0.18–1.04) for 75–80 vs. 65-69; and 0.47 (0.17–0.93) for 70–75 vs. 65–69 (supplemental online Table 4).

Interpretation

Overall, 12% of patients with CRC aged 65 or older were included in a clinical trial; the proportion ranged from 43% for the 65–69 age class to 6% for the patients aged 80 or older. Three-quarters of the patients were not included because they did not meet the eligibility criteria. With regard to the reasons for ineligibility, tumor characteristics,

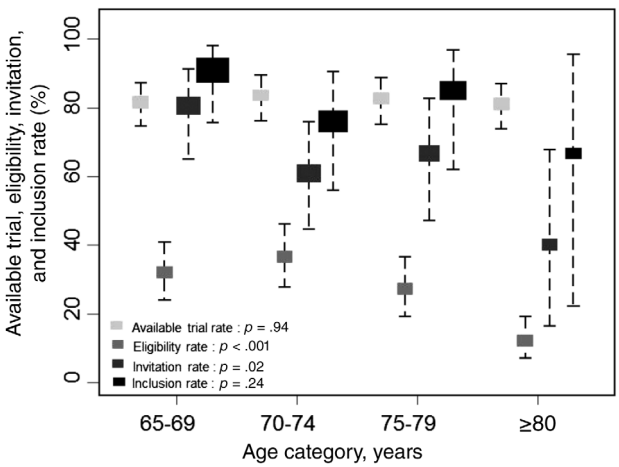

Figure 2. Trial availability, eligibility, invitation, and inclusion rates by in clinical trials age classes.
*Significant pairwise comparisons (p < .05): 80 years vs. 65–69; 80 years vs. 70–74, 80 years vs. 75–79.

Table 2. Inclusion and noninclusion criteria precluding eligibility by age class in the SAGE study, among patients with at least one available trial

Criteria[a]	65–69 yr (*n* = 128)	70–74 yr (*n* = 112)	75–79 yr (*n* = 110)	≥80 yr (*n* = 124)	*p* value[b]
Tumor characteristics (except stage and site), *n* (%)	49 (22)	55 (25)	49 (23)	66 (30)	.17
Examination required before inclusion or overly long time interval since examination, *n* (%)	25 (18)	37 (27)	28 (21)	46 (34)	.10
Previous/concomitant cancer treatment or excessively short time interval since treatment cessation, *n* (%)	29 (28)	19 (18)	23 (22)	34 (32)	.53
Performance status >2 or 1 depending on trial, *n* (%)	12 (17)	12 (17)	14 (21)	31 (45)	.05
Comorbidities, *n* (%)	10 (21)	14 (29)	4 (8)	20 (42)	.12
Altered hematological, hepatic, or renal biomarkers, *n* (%)	12 (25)	12 (25)	7 (15)	16 (35)	.8
Age limit, *n* (%)	5 (14)	5 (14)	11 (31)	15 (41)	.08
History of cancer, *n* (%)	3 (15)	4 (20)	3 (15)	10 (50)	.33
Comedication conflicting with the investigational treatment, *n* (%)	1 (17)	2 (33)	1 (17)	2 (33)	
No contraception (for men), *n* (%)	0	2 (50)	2 (50)	0	
Undetermined reasons, *n* (%)	8 (57)	1 (7)	1 (7)	4 (29)	

[a]Not mutually exclusive.
[b]Chi-square or Fischer exact test.

the absence of an examination required for inclusion, or an excessively long time interval between this examination and the inclusion period and a previous or concomitant incompatible cancer treatment were more frequently mentioned than the patient's comorbidities, PS, or age. Fourteen percent of trials exclude older adults on age criteria alone, and one trial was reserved for older patients (>75 years). Patients aged 80 or older were less likely to be eligible than other over-65 older age groups. Of the eligible patients, one-third had not been invited to participate in a trial, and about 20% of the invited patients were not included. Patients aged 80 or older were less likely to be invited to participate than other over-65 older age groups, even after the PS was taken into account [17].

Our results suggest that the strictness of trial eligibility criteria has not changed over time. Despite more than 20 years of recommendations and calls by researchers, regulatory agencies, and international societies to promote the inclusion of older patients in clinical trials (to match real life more closely), today's trials are still hindered by highly restrictive eligibility criteria [18, 19]. We found that 14% of today's trials still had an upper age limit (70 or 75 years), and only one was reserved for patients older than 75 years. In 109 trials published between 2007 and 2010, 20% excluded patients above a specified age. This suggested that there is little improvement toward no upper age limit in clinical trials [20].

The reasons for ineligibility were primarily cancer-related characteristics and secondarily comorbidities and PS, as found in a study of 1,079 patients with breast cancer in eight centers in the U.S. [21]. Javid et al. found a significant difference in ineligibility rates between older (over 65) and younger (under 65) patients but did not study age classes within the older group. We found a difference between over 80s and under 80s. This finding agrees with a recent U.S. Food and Drug Administration analysis of the enrollment of older adults in clinical trials for cancer drug registration [22]. Javid et al. did not find any difference in invitation rates between older (over 65) and younger (under 65) patients—in contrast to a case-control study based on 10 Cancer and Leukemia Group institutions [23]. Regarding invitations to participate in a trial, we did not find a difference between the groups of patients between 65 and 79 years, but we did find a difference between over 80s and under 80s.

When invited, the vast majority of older patients participated to the trials. There was no difference in the acceptance rate between the age classes of older patients [21, 23]. As previously reported, this indicates that physicians were less likely to discuss clinical trial participation with older patients despite their eligibility for an available trial [21]. The reasons for patients' refusal to participate in a trial were similar to those reported in the literature [21].

Strengths and Limitations

The main strength of our study is its prospective, longitudinal design, with follow-up all along the inclusion pathway (trial availability, eligibility, invitation, and inclusion). Moreover, the target sample size was reached and the number of event per variable was over 10, leading to accurate estimations of inclusion rate and factors associated with trials' invitation [24].

The main limitation is that the setting of the study was a large metropolitan area (Greater Paris area) of one of the countries with a developed geriatric oncology system (France). Therefore, it is likely that participation of older patients in trials in other areas of France and in other countries might be different. Moreover, only one digestive surgery department participated to the study, leading to a probable overestimation of the proportion of patients with stage III and IV. Another limitation relates to the study's restriction to patients with CRC. However, as CRC is a common disease, with a median age at diagnosis of 72 and appearing about equally in men and women, and with active clinical research, it can therefore be considered as a good model to explore

Table 3. Characteristics of eligible patients invited vs. not invited to participate in a clinical trial (n = 127) in the SAGE study

Variables	Invited (n = 84), n (%)	Not invited (n = 43), n (%)	crude RR (95% CI),[a] n (%)	p value
Age (base level, 65–69 yr)	33 (39)	8 (19)	Reference	.01
70–74	25 (30)	16 (37)	0.56 (0.24–0.97)	
75–79	20 (24)	10 (23)	0.54 (0.21–0.99)	
≥80	6 (7)	9 (21)	0.18 (0.04–0.61)	
Sex, male vs. female	46 (55)	23 (53)	1.01(0.71–1.24)	.99
Living alone	27 (33)	12 (28)	0.9 (0.57–1.19)	.56
Living at home	74 (89)	38 (88)	1.24 (0.80–1.44)	.23
Presence of a caregiver, yes vs. no	54 (66)	29 (71)	0.99 (0.66–1.25)	.97
Home-to-hospital distance (base level <5 km), km	24 (29)	7 (17)	Reference	.50
5–10	17 (20)	11 (26)	0.67 (0.28–1.12)	
10–15	12 (14)	8 (19)	0.73 (0.29–1.19)	
15–50	20 (24)	12 (29)	0.79 (0.36–1.20)	
≥50	10 (12)	4 (10)	1.08 (0.52–1.39)	
Cancer site (colon)	75 (89)	33 (77)	0.71 (0.34–1.10)	.16
Cancer stage (base level: 0, I, II)	5 (6)	6 (14)	Reference	.17
III	36 (43)	17 (40)	1.38 (0.99–1.49	
IV	43 (51)	20 (47)	1.37 (0.96–1.48)	
Performance status (base level: 0)	36 (43)	7 (17)	Reference	.012
1	41 (49)	28 (67)	0.45 (0.20–0.82)	
≥2	7 (8)	7 (17)	0.46 (0.14–0.96)	
Comorbidities	56 (67)	31 (74)	0.75 (0.43–1.07)	.14
BMI, base level (21–24.9), kg/m^2	31 (38)	16 (37)	Reference	
<21 (underweight)	14 (17)	15 (35)	0.66 (0.32–1.05)	.09
≥25 (overweight and obesity)	37 (45)	12 (28)	1.08 (0.72–1.32)	
Weight loss	50 (60)	26 (60)	1.16 (0.86–1.34)	.26
Frailty screening (G8 score ≤14 out of 17)	57 (70)	27 (84)	0.92 (0.53–1.20)	.29

[a]Hierarchical univariate logistic regression, with the patient at level 1 and the center at level 2; odds ratios were converted into relative risks.
Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

the issue of underrepresentation of older patients in clinical trials. Finally, we cannot exclude the possibility that the trial offer may be underestimated as it was based on a direct question to the physician. However, as the design was prospective, memory bias is probably weak.

Implications

Firstly, our results indicate the need to better distinguish between age classes of older patients. A single pooled subgroup of older patients aged 65 and older is too heterogeneous. Our results suggest that barriers to participation of older patients to trials are particularly marked at 80 years or older. Secondly, our results emphasize the need for more specific randomized controlled trials for older patients and in particular for patients over 80 years with pragmatic inclusion criteria and endpoints. [12, 16, 18, 25, 26] Large prospective observational cohorts with a precise follow-up of toxicity, functional decline, and quality of life may also constitute one way of generating more data on the risk-benefit ratio for cancer treatments in older patients [3, 27]. Another solution is to promote the existence of a prespecified subgroup of patients aged 80 or older in all-ages randomized controlled trials. Educational strategies to improve knowledge and attitudes of physicians toward older patients may also be helpful [28]. Finally, clinical research assistants and navigator-nurses dedicated to inclusion of older patients in clinical trials may help to increase their inclusion by removing organizational barriers and offsetting the lack of time of physicians.

Conclusion

Three-quarters of patients aged 65 and older were not included in a clinical trial because they failed to meet the eligibility criteria. Few ongoing trials are dedicated to older patients. We found that one-third of the eligible patients were not invited to participate in a clinical trial and that about 20% of invited patients were not included. Patients aged 80 or older were significantly less likely to be eligible for a trial and invited to participate in a trial.

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The investigator gave verbal information to the patient and obtained (or not) the patient's verbal consent to participation. Under French law, written, informed consent is not required for noninterventional studies. The protocol was approved by the appropriate ethics committee (CPP Ile-de-France IV, Paris, France). The SAGE cohort study was registered at ClinicalTrials.gov (NCT01754636).

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Disclosures

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