THERAPEUTIC ADVANCES in
Medical Oncology

Review

Management of esogastric cancer in older patients

Ther Adv Med Oncol

2024, Vol. 16: 1–14

DOI: 10.1177/17588359241272941

Thomas Aparicio, Anna Carteaux-Taieb, Amélie Arégui, Janina Estrada, Geoffroy Beraud-Chaulet, Virginie Fossey-Diaz, Pascal Hammel and Pierre Cattan

***Abstract*:** Although esogastric cancers often affect patients over 75, there are no specific age-related guidelines for the care of these patients. Esogastric cancers have a poor prognosis and require multimodal treatment to obtain a cure. The morbidity and mortality of these multimodal treatments can be limited if care is optimized by selecting patients for neoadjuvant treatment and surgery. This can include a geriatric assessment, prehabilitation, renutrition, and more extensive use of minimally invasive surgery. Denutrition is frequent in these patients and is particularly harmful in older patients. While older patients may be provided with neoadjuvant chemotherapy or radiotherapy, it must be adapted to the patient's status. A reduction in the initial dose of palliative chemotherapy should be considered in patients with metastases. These patients tolerate immunotherapy better than systemic chemotherapy, and a strategy to replace chemotherapy with immunotherapy whenever possible should be evaluated. Finally, better supportive care is needed in patients with a poor performance status. Prospective studies are needed to improve the care and prognosis of elderly patients.

Keywords: chemotherapy, esophagus cancer, gastric cancer, geriatric evaluation, older patients, surgery

Received: 6 April 2024; revised manuscript accepted: 17 July 2024.

Correspondence to:
Thomas Aparicio
Gastroenterology Department, Saint Louis Hospital, APHP, Université Paris Cité, 1 Avenue Claude Vellefaux, Paris 75475, France
thomas.aparicio@aphp.fr

Anna Carteaux-Taieb
Pierre Cattan
Department of Digestive Surgery, Saint Louis Hospital, APHP, Université Paris Cité, Paris, France

Amélie Arégui
Virginie Fossey-Diaz
Paris Nord Oncogeriatrics Coordination Unit, Bretonneau Hospital, APHP, Paris, France

Janina Estrada
Geriatric Out-Patient Unit, Bretonneau Hospital, APHP, Paris, France

Geoffroy Beraud-Chaulet
Pascal Hammel
Digestive and Medical Oncology Department, Paul Brousse Hospital, APHP, Paris-Saclay University, Villejuif, France

Introduction

Because of the aging of the global population, the proportion of patients with digestive cancer who are over 75 will increase. Unlike colorectal cancer, which has data specific to elderly patients, very few studies have been performed in other digestive cancers in this population.[1,2] Moreover, the management of non-colorectal digestive cancers is often more complex. Because of the frequently poor performance status and severe comorbidities, up to 25% of patients with esogastric cancers receive palliative care alone.[3] A geriatric assessment and intervention are essential to manage older patients with esogastric cancer.

The aim of this review is to clarify existing knowledge on the management of esogastric cancers in older patients. The main limitation of this review is the heterogeneity of the definition of the old population across the studies. Unfortunately, the study focusing on the population over 75 is scarce.

Epidemiology

Stomach and esophageal cancers are the 6th and 10th most common cancers, respectively, worldwide. Stomach cancers are especially frequent in Asia and Eastern Europe, and esophageal cancers are in Asia and Africa. Stomach and esophageal cancers are the fourth and sixth leading causes of death worldwide.[4] In a Swedish population study, 56% of patients with esophageal cancer were over the age of 70. While the incidence of squamous cell carcinoma of the esophagus is decreasing, in older men in particular, at the end of the 20th-century adenocarcinoma markedly increased and has recently stabilized. The incidence of esophageal adenocarcinoma has increased moderately in women over 70.[5] In France a national estimate in

2018 showed that 45% of patients with esophageal cancers are over 70.[6] Fifty-seven percent of gastric cancer patients are over 70 with an even higher proportion in women (62%).[6] The incidence of gastric cancer is decreasing worldwide except in patients under 40.[7]

Geriatric specificities of esogastric surgery

After major surgery, all patients experience a decline in their physiological reserves and their functional capacity, which increases the risk of postoperative complications. This may also result in slower and sometimes incomplete recovery that can make postoperative adjuvant chemotherapy impossible. A prehabilitation program including physical exercise training, nutritional interventions, and psychological support can improve physiological reserve/functional capacity to facilitate a more rapid and complete postoperative recovery. Moreover, prehabilitated patients may have a better chance of overcoming postoperative complications and of survival,[8] as well as of obtaining long-term functional independence and quality of life.[9] This is especially true in older patients. Indeed, the only positive randomized controlled trials testing whether prehabilitation helps reduce postoperative complications and maintains quality of life were performed in older patients (mean age of 71 years in the study of Barberan-Garcia et al.[9] study and 73 years in Berkel et al.[10] study). Improving postoperative recovery[11] should be part of patient care, so that one program leads to the next, followed by surgery, with a minimum of interruption.

The preoperative nutritional status in patients with digestive cancer is a prognostic factor for postoperative morbidity. Because this is even more important in older patients, who are more frequently malnourished for multifactorial reasons, this event should be systematically evaluated.[12] Conventional preventive or curative measures (food supplements, enteral, or parenteral artificial nutrition) must be begun to reverse malnutrition with special attention to the specific needs of the elderly (compliance, management of catheters, and tubes). Optimal care should combine nutritional, functional, and muscular management.

Cognitive disorders are a specific postoperative complication in geriatric patients. The incidence of postoperative confusion is 15% following planned surgery and 20% for the same procedure under emergency conditions.[13] Cognitive disorders are associated with higher postoperative mortality (19% vs 8%) and length of hospital stay (21 vs 8 days).[13] The risk factors of confusion are older age, high American Society of Anesthesiologists (ASA) score, low body mass index (BMI), low albumin, intraoperative hypotension, intraoperative blood transfusions, and a history of excessive alcohol consumption.[14] It is important to avoid prescribing drugs that can favor this syndrome (e.g. tramadol, psychotropic drugs, or proton pump inhibitors). The prevention and treatment of postoperative delirium is mainly based on non-pharmacological, multicomponent measures. In cases of severe agitation, when these measures are ineffective or impractical, minimal doses of antipsychotic treatment may be considered for the shortest possible duration.[15]

Besides specific measures to prevent and manage cognitive disorders, postoperative management of older patients should also be based on the modern notion of "Fast-Track Surgery" with the least aggressive surgery possible (short incisions or laparoscopy, no or brief drainage, early lifting and refeeding, morphine sparing for postoperative analgesia, early mobilization, and oral nutrition). This method has been validated in the general population undergoing digestive surgery, and may also be applied to older patients as long as the nursing teams can manage it.[16,17]

Cancers of the esophagus

Surgical treatment

Esophagectomy for cancer is one of the most morbid procedures in digestive cancer surgery, with high risks of major postoperative complications, such as anastomotic fistula, cardio-respiratory failure, hemorrhage, and a non-negligible risk of death, even in experienced centers. A large retrospective Japanese study evaluating patients who underwent esophagectomy for cancer showed that patients older than 75, and especially those over 80, underwent neoadjuvant treatment and extensive surgical procedures less often than younger patients, with a poorer prognosis.[18] This study has enrolled 509 (70.5%) patients under 70, 117 (16.2%) patients from 70 to 75, 73 (10.1%) patients from 75 to 80, and 23 (3.2%) patients over 80.

Whether surgery presents a higher risk in elderly patients is the subject of debate. The results probably depend on the method of selection and preoperative preparation as well as the surgical approach, in particular the use of minimally invasive procedures. Most series show that morbidity and mortality rates are higher in older patients.[18–20] A monocentric study on 32 (6.4%) patients ⩾80 years shows a greater risk of complications in the immediate postoperative period due to the physiological changes that occur with age including a reduction in functional reserves compared to 468 (93.6%) younger patients.[21] In particular, heart failure (13% vs 3%), respiratory failure, and renal failure are more frequent in older patients with a cutoff of 65 years old.[22] However, one study in 432 patients showed that there was no significant difference in the rate of surgical complications using a cutoff of 75 years old (13.7% of the total number of patients) after adjustment with a propensity score.[23] The rate of pneumopathy (16% vs 12%), arrhythmia (12% vs 7%), and confusion (4% vs 2%) was slightly higher in patients over the age of 75, but the difference was not significant (Dindo-Clavien grade 2: 44% vs 36%, $p = 0.34$ or Dindo-Clavien grade 3: 8% vs 12%, $p = 0.44$), re-operation rate (4% vs 6%, $p = 0.59$), postoperative mortality rate at 90 days (2% vs 0%, $p = 0.13$), and length of hospital stay (26 vs 28 days, $p = 0.39$). The use of minimally invasive surgery during esophagectomy may decrease the rate of postoperative complications[24,25] and increase the postoperative quality of life.[25] A recent series showed that minimally invasive esophagectomy is safe and feasible in older patients and a propensity score matching analysis showed that the short- and long-term outcomes of minimally invasive esophagectomy were similar in older (75-year-old, 29 patients, 14% of all the patients) versus younger patients.[26]

The difference in long-term survival between older and younger patients after esophagectomy is controversial and depends on the study.[27–29] However, as preoperative patient selection and postoperative care (particularly rehabilitation and better multidisciplinary management) have improved, the 5-year survival rate has become similar. Indeed, a study of 500 patients showed that there was no significant difference in the 30-day mortality rate (0.6% in the two groups) or the overall survival rate (53.2 ± 9.1 vs 77.6 ± 4.8 months, $p = 0.58$), in patients over or under 80 years old.[21] Nevertheless, patients over 80 years old are probably highly selected as they represent only 6.4% of all the patients.

This suggests that esophagectomy is possible in older patients if the three following factors are respected:

(1) Careful selection based on a geriatric assessment and preoperative management including nutritional management, optimization of comorbidities, full anesthesiologist evaluation, and prehabilitation.
(2) Optimal perioperative care with experienced anesthesiologists and surgeons for esophageal surgery with access to minimally invasive surgery if possible.
(3) Postoperative management with trained intensive care specialists and rapid, minimally invasive management of surgical complications.

Neo-adjuvant and adjuvant treatment for resectable tumors

Overall survival in elderly patients with resectable and non-resectable localized tumors is presented in Table 1 according to type of treatment, with or without surgery. Most studies performed in older patients show that a combination of chemoradiotherapy (CRT) and surgery is more beneficial than CRT alone. Neoadjuvant CRT followed by surgery is indicated for resectable T3–T4 tumors and/or tumors with lymph node invasion without distant metastases.[30] One meta-analysis has shown that this treatment protocol reduces the risk of mortality by 22%, compared to surgery alone (20% for squamous cell carcinomas and 25% for adenocarcinomas).[31] In one retrospective German study, a reduction in the dose of chemotherapy was required in up to 40% of patients over 75 years, mainly due to toxicity, and was associated with poorer treatment efficacy.[32] Although the recommended treatment combining paclitaxel and radiotherapy (CROSS regimen) appears to be well tolerated, including in patients over 75 with a good performance status or well-selected patients over 70,[33,34] there are no specific prospective geriatric studies evaluating this treatment.

CRT alone with salvage surgery in case of a residual tumor or local recurrence is a therapeutic option in patients with resectable squamous cell carcinomas and high surgical risk.[37] However, a

Table 1. Treatment results for resectable and non-resectable esophageal localized tumors in older patients.

Study	*N* older patients (% of total number)	Median age	Histology	Treatment arm	Overall survival	*p*
Bostel et al., 2023[32] Retrospective study	161 (100%)	73	100% Squamous cell	CRT CRT + surgery	5 years OS: 9% 5 years OS: 41%	0.002
Cooper et al., 2021[34] Retrospective study	65 (32%)	73.7	84% adenocarcinoma	CRT + surgery ⩾70 years CRT + surgery <70 years	1 year OS: 82.7% 1 year OS: 90.4%	0.24
Koëter et al., 2018[35] Registry study	250	81.6	Adenocarcinoma	CRT + surgery	3 years OS: 51.2%	<0.001
	475				Surgery alone	3 years OS: 29.5%
	261				CRT alone	3 years OS: 11.6%
	59	81.3	Squamous cell carcinoma	CRT + surgery	3 years OS: 50.2%	0.267
	55				Surgery alone	3 years OS: 40%
	144				CRT alone	3 years OS: 36.8%
Kelly et al., 2021[36] Prospective randomized trial	287 (36%)	<65 ⩾65	Adenocarcinoma and squamous cell carcinoma (71% and 29%)	Adjuvant nivolumab Placebo Adjuvant nivolumab Placebo	24.4 months 10.8 months 17 months 13.9 months	HR = 0.65 (0.51–0.84) HR = 0.80 (0.57–1.12)

CRT, chemoradiotherapy; HR, hazard ratio; OS, overall survival.

Dutch database analysis has suggested that survival in patients over 75 with squamous cell carcinoma is similar after receiving preoperative CRT, surgery alone, or CRT alone. On the other hand, survival in patients over 75 with esophageal adenocarcinoma who received preoperative CRT was better than in those treated with surgery or radiotherapy alone.[35]

Adjuvant treatment with anti-PD-L1 immunotherapy (nivolumab) is indicated in patients with R0 surgical resection after preoperative CRT but with a tumor remnant in the surgical specimen. Median recurrence-free survival was doubled compared to observation alone (22.4 vs 11 months), but with less benefit in patients over 65 (HR = 0.65 (0.51–0.84) if <65 years and HR = 0.80 (0.57–1.12) if >65 years).[36]

Treatment of locally advanced tumors

A retrospective analysis of the SEER database of locally advanced unresectable but non-metastatic esophageal cancer in patients ⩾65 years showed that the results of CRT were better than radiotherapy alone, even in the oldest patients over 85, both for overall and cancer-specific survival.[38] A Chinese phase III study compared CRT with S-1 to radiotherapy alone in esophageal cancer patients over the age of 70. Two-year survival was improved in the CRT arm (53% vs 36%), with no increase in toxicity except for leukopenia.[39] Another retrospective study in patients ⩾70 years suggests that doublet CRT does not improve progression-free survival or overall survival compared to chemotherapy alone.[40] In a French series of 109 patients over 70 treated with CRT and cisplatin for locally advanced esophageal cancer, the Charlson co-morbidity score was significantly associated with treatment tolerance. Independent predictors of overall survival were a complete response, CRT dose completion >80%, and a Charlson score <2. The median Charlson score at inclusion in that study was 1 suggesting a selection of fit patients.[41] A Japanese retrospective study in patients over 80 showed that denutrition was an important prognostic factor for both overall survival and progression-free survival in patients treated with CRT alone.[42] The combination of immunotherapy and radiotherapy is currently being evaluated in patients with locally advanced tumors.

All these data show the importance of prehabilitation before and during chemotherapy in older patients and especially nutritional support, raising the question of CRT with chemotherapy alone rather than polychemotherapy in this population. Ideally, comorbidities and nutritional status should be assessed as part of a systematic geriatric evaluation to establish the best strategy for the patient's treatment.

Treatment of metastatic tumors

Very few studies have evaluated palliative chemotherapy in metastatic esophageal squamous cell carcinoma and there are no specific data for older patients. Chemotherapy regimens are based on fluoropyrimidine, platinum salts, and taxanes. Patients with adenocarcinomas are usually treated using the same chemotherapies as those for gastric adenocarcinomas. Thus, the indication for palliative chemotherapy must be discussed on a case-by-case basis in a multidisciplinary meeting.

Several recent studies have demonstrated the efficacy of immunotherapy combined with platinum-based chemotherapy as a first-line treatment of metastatic esophageal squamous cell carcinoma.[43,44] In the CHECKMATE 648 study, overall survival with a combination of nivolumab (anti-program death ligand 1 (PD-L1) antibody) plus ipilimumab (anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody) without chemotherapy was comparable to that with a combination of nivolumab plus chemotherapy, and better than that with chemotherapy alone (12.8 vs 13.2 vs 10.7 months).[44] In the KEYNOTE 590 study comparing a combination of pembrolizumab (anti-PD-L1 antibody) plus chemotherapy to chemotherapy alone, immunotherapy was more beneficial for progression-free survival and overall survival in patients aged over 65 than in younger patients.[43]

The RAMONA study evaluated nivolumab alone or in combination with ipilimumab in patients over 65 as second-line treatment. Median overall survival was 7.2 months, which was significantly higher than that of a historical cohort (5.9 months, $p = 0.0063$).[45]

Overall, immunotherapy appears to be as effective in older patients with metastatic esophageal cancer as in younger patients. Immunotherapy alone could be an interesting option in frail patients and will be soon explored in the PRODIGE 102—SAFE-OESO trial.

Gastric adenocarcinoma

Surgical treatment

Gastrectomy is a therapeutic option for gastric cancer which is also associated with significant morbidity and mortality, although less than esophagectomy. Thus, a multidisciplinary evaluation is required before deciding to operate on an older patient. One retrospective study evaluated three age groups: <60, 60–75, and >75 years and found morbidity of 37%, 45%, and 48%, and postoperative mortality of 0%, 1%, and 8%, respectively ($p < 0.05$).[46] In that study recurrence tended to be lower in older patients (35%, 37%, and 27%, respectively ($p < 0.437$) and 5-year cancer survival was similar among the groups (61%, 53%, and 61%).[46] In another retrospective study of 1118 patients with 249 over the age of 75, age was not a prognostic factor for postoperative mortality (3% in both groups), morbidity (18% vs 20%), or specific cancer mortality (5-year survival of 47% and 54%, respectively).[47]

Laparoscopic gastrectomy should be chosen whenever possible because it reduces blood loss, and postoperative complications, allows a return to oral feeding more quickly, and reduces the length of hospital stay compared to open laparotomy, with a comparable R0 resection rate.[12,48,49] Robotic surgery seems to be better than minimally invasive surgery for lymphadenectomy[50] and postoperative complications.[51] Older patients are less likely to undergo total gastrectomy and lymph node dissection than patients under 75,[46,47] in particular, because the esophagus is fragile, increasing the risk of esophageal anastomosis leakage. However, the complications of subtotal and total gastrectomy do not justify the risk of obtaining R1 margins by performing a partial gastrectomy. D2 lymph node resection without splenectomy is recommended regardless of age.[52]

As for esophagus, careful selection and pre-habilitation of older patients are crucial before surgical resection in order to avoid postoperative morbidity.

Preoperative chemotherapy

The prognosis of gastric adenocarcinoma is poor, even with R0 resection. The recommended medical treatment is perioperative chemotherapy.[52] Combinations of 5-fluorouracil (5FU) and cisplatin,[53] or epirubicin, capecitabine, and cisplatin[54] have been shown to improve survival compared to surgery alone. The regimen combining 5FU plus oxaliplatin and docetaxel (FLOT) is now recommended because it was found to be superior to the combination of epirubicin, capecitabine, and cisplatin.[55] The results of perioperative chemotherapy are provided in Table 2.

A retrospective analysis evaluating a combination of perioperative 5FU plus oxaliplatin (FOLFOX) in 109 patients, 53% of whom were over 65, showed comparable results to those obtained with other perioperative chemotherapy regimens.[57] A randomized phase II trial in 44 patients over age 65 evaluated the perioperative combinations of 5-FU plus oxaliplatin and the FLOT regimen. Hematological and digestive toxicities, as well as the incidence of impaired quality of life (54% vs 23%), and postoperative morbidity (60% vs 35%), were also more frequent with FLOT. There was a trend toward better progression-free survival in the FLOT arm (21 vs 12 months, $p = 0.09$).[56] These results suggest that a regimen combining 5FU plus oxaliplatin may be an alternative to FLOT in elderly or frail patients. In a Japanese study that showed that S1 was an effective adjuvant treatment, the efficacy of chemotherapy in 25% of patients between 70 and 80 years old was similar to that in younger patients.[58]

The objectives of neoadjuvant chemotherapy are (1) to obtain tumor reduction to facilitate surgery, and (2) to have a better chance of treating micrometastases, as neoadjuvant is more feasible than postoperative chemotherapy. These objectives must be considered in relation to the patient assessment. The dose and schedule of chemotherapy must be sufficiently well tolerated to be effective, and not result in complications that could prevent implementation of the surgical plan. Thus, the decision to administer neoadjuvant chemotherapy or not is crucial and should be made by a multidisciplinary team, following an oncogeriatric assessment whenever possible.

The combination of immunotherapy with neoadjuvant chemotherapy is under investigation and may soon become a new therapeutic option.

The rate of tumors with DNA repair abnormalities (deficient mismatch repair (dMMR)/microsatellite instability (MSI)) is as high as 17% in patients over 70.[59] Perioperative chemotherapy has not been found to be beneficial in this subset

Table 2. Perioperative chemotherapy for gastric adenocarcinoma in older patients.

Study	*N* older patients	Median age	Treatment arm	Overall survival
Cunningham et al., 2006[54] Prospective randomized trial	<60 years: *n* = 108 *n* = 104 60–69 years: *n* = 91 *n* = 95 ⩾70 years: *n* = 51 *n* = 54	62	5FU + cisplatin + epirubicin + surgery Surgery alone 5FU + cisplatin + epirubicin + surgery Surgery alone 5FU + cisplatin + epirubicin + surgery Surgery alone	56% of death 72% 62% 62% 63% 67%; *p* for trend = 0.43
Lorenzen et al., 2013[56] Prospective randomized trial	21 22	69 71.5	5FU + oxaliplatin + docetaxel 5FU + oxaliplatin	2 years OS: 78% 2 years OS: 56% *p* = 0.059
Al-Batran et al., 2019[55] Prospective randomized trial	<60 years: *n* = 155 *n* = 160 60–69 years: *n* = 116 *n* = 113 ⩾70 years: *n* = 85 *n* = 87	62	5FU + oxaliplatin + docetaxel Fluoropyrimidine + cisplatin + epirubicin 5FU + oxaliplatin + docetaxel Fluoropyrimidine + cisplatin + epirubicin 5FU + oxaliplatin + docetaxel Fluoropyrimidine + cisplatin + epirubicin	HR = 0.770 HR = 0.797 HR = 0.723 *p* = 0.94

5FU, 5-fluorouracil; HR, hazard ratio.

of patients.[60] On the other hand neoadjuvant immunotherapy resulted in a complete pathological response in 58.6% of patients in a phase II trial.[61] Thus, dMMR/MSI status must be assessed as early as the first endoscopic biopsy.[62] Overall, an immunotherapy-based therapeutic strategy could be of interest to elderly patients, especially frail individuals with dMMR/MSI tumors because it eliminates the need for gastrectomy and obtains a high rate of tumor response.

Palliative chemotherapy

In the past decade, chemotherapy for gastric adenocarcinoma has made much less progress than that of colorectal cancer. Median survival is still less than 1 year in most studies. The results of palliative treatment in older patients are presented in Table 3. Recommendations are based on polychemotherapies combining fluoropyrimidine plus platinum plus epirubicin or combining fluoropyrimidine plus docetaxel plus cisplatin, which are highly toxic, and on the combination of trastuzumab (anti-HER2 monoclonal antibody) plus chemotherapy in case of HER2 receptor overexpression present in about 15% of gastric adenocarcinomas.[52] The recent phase III trial PRODIGE 51—FFCD 1601—GASTFOX showed an improvement in overall survival using the triplet oxaliplatin plus 5FU and docetaxel compared to FOLFOX (15.1 vs 12.6 months, $p = 0.048$).[63] Nevertheless, there is no significant benefit for overall survival of triplet chemotherapy in the subgroup of patients over 65 (Table 3).

There are very few studies specifically evaluating elderly patients. One phase II study evaluated the FOLFIRI schema in 42 patients over 70 with metastatic gastric cancer. The results showed a 1-year overall survival of 41.5%, a 1-year progression-free survival of 31.8%, and an objective response rate of 26%. Thanks to a geriatric assessment that was repeated during the study, patient autonomy was preserved and nutritional status improved after 4 months of treatment.[71]

A phase III study compared 5-FU plus cisplatin and 5-FU plus oxaliplatin in 220 patients. There were significantly fewer serious adverse events in the oxaliplatin group (9% vs 19%), with fewer hematologic, digestive, and renal toxicities but as expected, more neurological toxicity. Significant improvement was found with oxaliplatin in the subgroup of patients over 65 (43% of the population), for progression-free survival (6 vs 3.1 months, $p = 0.029$) and overall survival (13.9 vs 7.2 months, $p = 0.02$).[64]

Another randomized phase II trial in 143 patients over age 65 evaluated the combination of 5-FU plus oxaliplatin with or without docetaxel. The results suggest that the triple combination was

Table 3. Palliative treatment for metastatic esogastric adenocarcinoma in older patients.

Study	Age	*N* (%)	Treatment arm	Overall survival	*p* or HR (95% CI)
Al-Batran et al., 2008[64] Randomized prospective trial	⩾65 years *n* = 94/220 (42.7%)	46 48	5FU + oxaliplatin 5FU + cisplatin	13.9 months 7.2 months	*p* = 0.083
Bang et al., 2010[65] Randomized prospective trial. HER2 positive	⩾60 years *n* = 305/584 (52%)	<60 years *n* = 279 ⩾60 years *n* = 305	Fluoropyrimidine + cisplatin + trastuzumab Fluoropyrimidine + cisplatin Fluoropyrimidine + cisplatin + trastuzumab Fluoropyrimidine + cisplatin	– – – –	HR = 0.84 (0.62–1.14) HR = 0.66 (0.49–0.88)
Al-Batran et al., 2013[66] Randomized prospective trial	Median 70 years	72 71	5FU + oxaliplatin + docetaxel 5FU + oxaliplatin	17.3 months 14.5 months	*p* = 0.39
Shitara et al., 2020[67] Randomized prospective trial. CPS ⩾10	<65 years >65 years	291 216	Fluoropyrimidine + cisplatin + pembrolizumab Fluoropyrimidine + cisplatin Fluoropyrimidine + cisplatin + pembrolizumab Fluoropyrimidine + cisplatin	– – – –	HR = 0.75 (0.59–0.97) HR = 0.96 (0.72–1.29)
Hall et al., 2021[68] Randomized prospective trial	Median 76 years Median 76 years Median 77 years	170 171 173	Oxaliplatin 130 + capecitabine 625[a] oxaliplatin 100 + capecitabine 500[b] oxaliplatin 80 + capecitabine 375[c]	– – –	2 vs 1 HR = 1.09 (0.88–1.36) 3 vs 1 HR = 1.14 (0.92–1.41)
Janjigian et al., 2021[69] Randomized prospective trial. CPS ⩾5	<65 years >65 years	552 (57.8%) 403 (42.2%)	XELOX or FOLFOX + nivolumab XELOX or FOLFOX XELOX or FOLFOX + nivolumab XELOX or FOLFOX	14.8 months 11.0 months 14.3 months 11.2 months	HR = 0.69 (0.56–0.84) HR = 0.72 (0.57–0.91)
Shitara et al., 2023[70] Randomized prospective trial. Claudin 18 positive	⩽65 years >65 years	362 (64%) 203 (36%)	5FU + oxaliplatin + zolbetuximab 5FU + zolbetuximab 5FU + oxaliplatin + zolbetuximab 5FU + oxaliplatin	– – – –	HR = 0.74 (0.56–0.98) HR = 0.76 (0.53–1.09)
Zaanan et al., 2023[63] Randomized prospective trial	<65 years >65 years	266 (53%) 240 (47%)	5FU + oxaliplatin + docetaxel 5FU + oxaliplatin 5FU + oxaliplatin + docetaxel 5FU + oxaliplatin	14.1 months 10.8 months 16.3 months 14.4 months	HR = 0.74 (0.57–0.97) HR = 0.91 (0.68–1.21)

[a]Oxaliplatin 130 mg/m^2 on day 1 and capecitabine 625 mg/m^2 twice a day on days 1–21.
[b]Oxaliplatin 100 mg/m^2 on day 1 and capecitabine 500 mg/m^2 twice a day on days 1–21.
[c]Oxaliplatin 80 mg/m^2 on day 1 and capecitabine 375 mg/m^2 twice a day on days 1–21.
CI, confidence interval; CPS, combined positive score; 5FU, 5-fluorouracil; HR, hazard ratio.

more effective, with an increase in progression-free survival from 6.7 to 9.1 months and overall survival from 14.4 to 17.3 months.[66] Although there was more toxicity (alopecia, neutropenia, diarrhea, and nausea) this did not influence the rates of treatment discontinuation or toxic deaths. These data suggest that intensive chemotherapy should not be ruled out in carefully selected older patients. However, these results should be interpreted with caution in very old patients, because the median age in this trial was only 70.

A phase III trial evaluated elderly and frail patients with advanced gastroesophageal cancer to compare the effect of reduced-intensity chemotherapy with oxaliplatin and capecitabine (by 20% or 40%) and standard doses on quality of life and cancer control. An initially reduced dose was found to be non-inferior to a standard dose for progression-free survival with similar overall survival while all toxic effects were significantly decreased at reduced doses.[68]

Although there are no specific data on trastuzumab treatment in older patients with gastric HER-2 overexpression adenocarcinoma tumors the subgroup analysis in the TOGA trial showed a higher hazard ratio in favor of trastuzumab in patients over the age of 60.[65] The main risk of toxicity in older patients is cardiac. Thus, cardiac function should be assessed before trastuzumab is administered. Zolbetuximab, a monoclonal antibody targeting claudin-18 isoform 2 (CLDN18.2), has recently been shown to be effective in patients with CLDN18.2-positive tumors.[70] The efficacy of zolbetuximab was not confirmed in patients older than 75 (HR = 1.32 (0.58–3.00)), however, there were too few older patients ($n = 28$) enrolled in this study to draw firm conclusions.

Survival following immunotherapy combined with chemotherapy as a first-line treatment of metastatic esophageal adenocarcinoma was found to be better than chemotherapy alone.[56,57] In the CHECKMATE 649 trial, the efficacy of nivolumab combined with 5FU plus oxaliplatin was similar whatever the age, over 65 or younger, but once again, there were very few patients over the age of 70.[69] In the KEYNOTE-062 trial, the combination of pembrolizumab plus fluoropyrimidine and cisplatin was not more effective than chemotherapy alone in the subgroup of patients over 65.[67] Tolerance of oxaliplatin is better in older patients, thus allowing administration of higher doses than cisplatin, which may partly explain the different results of the two studies. The safety and efficacy of immunotherapy combined with chemotherapy in older and/or frail patients is not well documented. One retrospective study evaluated immunotherapy in patients over 70 treated for digestive cancer, in particular dMMR/MSI or hepatocellular carcinoma, and found that the efficacy and safety were similar to results in registration trials.[72] A prospective study of patients over 75 treated with immunotherapy and with a geriatric assessment is needed.

Conclusion

Although progress has been made in the management of cancer in older patients in recent years, in particular surgical treatment, overall these patients are still under-treated and do not yet receive optimal care. All older patients cannot tolerate aggressive cancer treatments, thus, therapeutic decisions must be made by a multidisciplinary oncology team including an oncogeriatrician. Age alone should not be used as unique predictor to choose treatment options, WHO performance status, comorbidities, and geriatric assessment are needed to define individual therapeutic strategies.

A geriatric evaluation can help improve patient selection for conventional treatments, as well as adapt the modalities in older patients and manage medical or social measures needed for their implementation. Overall, antitumoral treatment must be part of a care network involving the oncologist, general practitioner, geriatrician, and, whenever possible, home care or follow-up care facilities. Geriatric intervention improves survival in patients treated for cancer.[73] Co-management by surgeons and geriatricians is associated with a reduction in the 3-month mortality after surgery.[74] Prehabilitation before surgery could help increase the functional reserve in these patients, improve tolerance to the physiological stress of major surgery, and reduce the risk of postoperative complications.[75]

Finally, trials performed to determine therapeutic standards have mainly included patients under the age of 75. The recommended therapeutic strategies should be re-evaluated in older patients, especially the benefit/risk ratio. Prospective therapeutic trials specifically dedicated to older subjects, that consider both oncological and geriatric data (comorbidities and treatment, nutritional status, living conditions, maintenance of autonomy, and quality of life), are essential.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Thomas Aparicio: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Anna Carteaux-Taieb: Conceptualization; Data curation; Formal analysis; Investigation; Validation; Writing – original draft; Writing – review & editing.

Amélie Arégui: Conceptualization; Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Janina Estrada: Investigation; Writing – review & editing.

Geoffroy Beraud-Chaulet: Investigation; Writing – review & editing.

Virginie Fossey-Diaz: Formal analysis; Writing – review & editing.

Pascal Hammel: Conceptualization; Project administration; Supervision; Writing – review & editing.

Pierre Cattan: Formal analysis; Writing – review & editing.

Acknowledgments
To Mrs Dale Roche for English editing.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
T.A. is an Editorial Board Member of Therapeutic Advances in Medical Oncology and an author of this paper; therefore, the peer-review process was managed by alternative members of the board and the submitting editor has not been involved in the decision-making process. T.A. received honoraria from BMS, Pierre Fabre, Bayer, and MSD. P.H. received financial support from AstraZeneca and honoraria from Servier and Viatris. A.C.-T., A.A., J.E., G.B.-C., V.F.-D., and P.C. declare no conflict of interest.

Availability of data and materials
Not applicable.

ORCID iD
Thomas Aparicio https://orcid.org/0000-0001-8834-6927
Amélie Arégui https://orcid.org/0009-0001-5602-9561
Pascal Hammel https://orcid.org/0000-0002-4630-4996

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