Concurrent chemoradiation therapy tailored to the older adults with esophageal cancer: state of the art and the future

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Purpose: The aim of this study was to review the published literature addressing the question of whether geriatric assessment (GA) should be routinely applied in the treatment of older adults with esophageal cancer (EC) who have received definitive concurrent chemoradiotherapy (dCRT).

Materials and methods: A literature search of PubMed, Embase, and Cochrane Library was performed. Studies that contained original data outlining the inclusion and exclusion criteria, treatment compliance rate, and severe toxicity reports were reviewed. Additionally, criteria from ongoing clinical trials in the World Health Organization and National Institutes of Health registries were reviewed to evaluate the utilization of GA-related domains in elderly EC patients who received dCRT.

Results: Twenty-nine studies were identified based on the selection criteria: five were single-arm prospective studies, and the other studies were retrospective studies. All studies used chronological age and performance status as basic descriptors for this subpopulation. The comorbidity index and the malnutrition level were mentioned in several studies. However, factors such as “Demographic data and social support,” “Psychology,” “Polypharmacy,” and “Geriatric syndromes” were not described in any of the included studies. Unfortunately, the results were similar for the registered clinical trials. Finally, treatment compliance and toxicity profile were found to be acceptable in selected elderly EC patients.

Conclusion: The current experience for older adults with EC receiving dCRT is mainly based on the results of a series of retrospective studies. Ongoing clinical trials should routinely consider GA-related domains to select appropriate treatments for patients in the future.

Keywords: older adults, esophageal cancer, chemoradiotherapy, inclusion criteria, toxicity, geriatric assessment

Introduction

Esophageal cancer (EC) is a prevalent disease with a very poor prognosis. It is the fourth most common cause of cancer death in People’s Republic of China.¹² As life expectancy is expected to increase over time, the number of older adults with EC is likely to increase worldwide. However, due to the vast heterogeneity in the aging population, elderly patients are underrepresented in most clinical trials. How to best manage this specific population is still a great challenge. In a recently published study, 21,593 elderly (aged over 70 years) EC patients with clinical stage II or III cancer identified from the National Cancer Database were retrospectively analyzed. Demographic characteristics revealed that 37.1% (8,010/21,593) of patients had received definitive concurrent chemoradiotherapy (dCRT).³ Considering that some patients were diagnosed with clinical stage I or IVa cancer, we believe that more than 37.1%...
of elderly EC patients were recommended dCRT as the first-line of cancer therapy.

Currently, there is consensus within the geriatric oncology community that chronological age alone is a poor descriptor of the heterogeneity that exists within the aging process. Variation in physiological reserves, comorbidities, geriatric syndromes, and limited social support networks also contribute to the risk associated with aggressive treatment modalities. In light of these circumstances, the International Society of Geriatric Oncology (SIOG) and National Comprehensive Cancer Network established recommendations for geriatric assessment (GA) to help oncologists determine suitable treatment choices for older patients. However, the role of GA in the application of dCRT for elderly EC patients remains to be clarified.

Thus, the purpose of this study was to conduct a systematic review of all existing observational cohort studies on the use of GA in the treatment decisions for elderly EC patients receiving dCRT. However, due to the low number of previous studies that used GA in pretreatment evaluation, we summarized the inclusion and exclusion criteria and other important aspects related to GA, including treatment compliance and toxicity for older adults with EC, focusing on whether GA-related domains were routinely applied. We provide some potential suggestions for registered clinical trials in the future.

**Materials and methods**

**Search strategy and article selection**

A systematic literature search for articles published between January 1, 1990 and December 31, 2017 was conducted in PubMed, Embase, and Cochrane Library with the assistance of a research librarian. The primary outcome was to identify all publications containing original data on the use of dCRT in older adults with EC, including study inclusion and exclusion criteria, treatment compliance, and reports of severe toxicity. The following terms were used as search terms: (esophageal or oesophageal) and (cancer or carcinoma or neoplasm or tumor or tumour) and (aged or older or elderly) and concurrent and treatment. Exclusion criteria for search results were as follows: the study involved neoadjuvant chemoradiotherapy (nCRT) with surgery; the study was in Phase I; the study involved palliative chemoradiotherapy; the study was not published with the full text; the study was combined with nCRT or radiotherapy alone; and the study results were not reported exactly. The search did not restrict the type of publication but was limited to English language.

To identify ongoing clinical trials focusing on the efficiency and safety of dCRT for older adults with EC, the World Health Organization registry network (http://www.who.int/clinicaltrials regist y) and the National Institutes of Health (NIH) clinical trial registry (http://www.ClinicalTrials.gov) were searched on December 31, 2017, using the search terms “esophageal cancer” and “radiotherapy.” The search was limited to only interventional trials currently recruiting elderly EC patients or intending to start recruitment.

**Review methods**

The abstract of each article was first reviewed by the corresponding author (SW). Irrelevant citations were removed according to the selection criteria, thereby creating a preliminary set of potentially relevant publications. Then, the full-text articles were distributed to the review team along with an evaluation form customized for reviewing the GA-related domains previously mentioned: study selection criteria, reports of severe toxicity and treatment compliance (TS and MF). The evaluation results were compared and reevaluated until consensus was reached between the two reviewers. For ongoing clinical trials, the following data were also extracted from the registry website: registration number, country, chemotherapy regimen, inclusion age, and GA-related domains mentioned in the selection criteria.

To allow the combination of performance status data, a score of 100 on the Karnofsky Performance Scale Index (KPS) was considered equivalent to an Eastern Cooperative Oncology Group performance status (ECOG PS) scale score of 0; a score of 80–90 on the KPS was considered equivalent to an ECOG PS score of 1; and a score of 60–70 on the KPS scale was considered equivalent to an ECOG PS score of 2.7 GA-related domains were classified using the following categories: “demographic data and social support,” “comorbidity,” “functional status,” “cognition,” “psychology,” “nutrition,” “polypharmacy,” and “geriatric syndromes,” following the SIOG recommendations released in 2014. In the published reports, restrictions in selection criteria were labeled as “specific criterion mentioned in the report” or “not limited” or “not reported” for each category listed above. In the registered clinical trials, restrictions in selection criteria were labeled as “strict,” “mentioned,” or “not reported” for GA-related domains.

**Results**

**Description of studies and methodological issues**

After examination of the relevant abstracts and full-text articles by the review group, a total of 29 published studies involving 1,487 EC patients were incorporated into the systematic review. A flow diagram of citation retrieval and
selection is presented in Figure 1. The basic characteristics of patients and GA-related domains mentioned in the methods and results are summarized in Table 1.8–36 Of these 29 reports, 5 studies were single-arm prospective clinical trials and the other studies were retrospective studies. Of the five prospective studies, one study used radiation with concurrent targeted therapy of gefitinib. Patient sample size in the eligible studies ranged from 7 to 188. Nearly 84.4% (1,255/1,487) of patients were diagnosed with esophageal squamous cell carcinoma (ESCC). Eleven reports defined the chronological age of 70 as the cutoff age for older adults. Among studies, considerable variation was found across chemotherapy regimens, radiation therapy doses, and radiotherapy parameters. These methodological issues made comparing the results challenging both within study groups and between studies.

GA-related issues
Unfortunately, “demographic data and social support,” “psychology,” “polypharmacy,” and “geriatric syndromes” categories were not described in any of the selected studies (Table S1). Only one prospective study conducted by Servagi-Vernat et al8 used Folstein’s test as the GA for “Cognition.” The other domains are presented in the following.

Functional status
ECOG PS and KPS were the two most commonly used tools of functional status assessment in daily oncological practice. Among the 29 selected studies, 2 studies did not clearly report the functional status of elderly patients. For the remaining 27 studies, 15 studies used the basic ECOG PS score of 0–2 for inclusion, and 6 studies restricted the ECOG PS score to 0–1 for inclusion. Among the 16 studies that clearly demonstrated the proportion of performance status scores across patients, 77.2% (586/759) of the patients were assessed at an ECOG PS score of 0–1, and 173 patients were assessed at an ECOG PS score of 2–3. It is worth mentioning that only one prospective study, also conducted by Servagi-Vernat et al,8 used Instrumental Activity Of Daily Living as an additional instrument for evaluating functional status.

Comorbidity
Comorbidity is a characterization factor for elderly cancer patients. In this review, 18 studies mentioned comorbidities in enrolled patients. Among them, the Charlson Comorbidity Index (CCI), or its age-adjusted version (ACCI), was the most common tool for assessing comorbidity. In the five prospective studies, two clinical trials, both conducted by Servagi-Vernat et al,8 used inclusion criteria of CCI.
Table 1  Baseline characteristics of the published reports in elderly EC patients who received dCRT or concurrent radiation with targeted therapy (basic version)

| Study          | Study design | Histology (SCC/AC/other) | Age (range) | CT            | Radiation dose (Gy) | Comorbidity | Functional status (ECOG PS) | Cognition | Nutrition | Compliance |
|---------------|--------------|--------------------------|-------------|---------------|---------------------|--------------|--------------------------------|------------|------------|------------|
| Servagi-Vernat et al | Prospective | ≥75 (79.4–92)            | Single (DDP/OHP) | 50            | CCI ≤3              | 0–2 (23/7) 0–1/2 and IADL | Folstein's test | Weight loss ≤15% | 93.30%     |
| Ji et al      | Prospective  | ≥65 (65–80)              | Single (S-1)  | 54            | NR                  | 0–2 (16/14 0–1/2) | NR               | Weight loss ≤15% | 89.00%     |
| Xu et al      | Prospective  | ≥65 (65–83)              | Single (gefitinib) | 50.4          | NR                  | 0–2 (5.986 pt)    | NR               | NR               | 90%        |
| Zhang et al   | Prospective  | ≥65 (65–89)              | Double (TP/PF) | 60            | NR                  | 0–2 (63/7 0–1/2) | NR               | NR               | 90%        |
| Xu et al      | Prospective  | ≥65 (65–83)              | Single (DDP)  | 50            | CCI ≤4              | 0–2 (16/6 0–1/2) | NR               | NR               | 90%        |
| Song et al    | Prospective  | ≥60 (60–83)              | Double (5-FU + Tax) | 50.4          | NR                  | 0–2 (22/12 0–1/2) | NR               | NR               | 90%        |
| Zhao et al    | Prospective  | ≥70                      | Single (S-1)  | 60            | NL                  | 0–3 (63/7 0–1/2–3) | NR               | NR               | 90%        |
| Zhao et al    | Prospective  | ≥70                      | Single (S-1/Cape) | 61.6          | NL                  | 0–1 (0–1/2–3)    | NR               | NR               | 90%        |
| Lü et al      | Retrospective| ≥65 (65–83)              | Single (S-1)  | 54–60         | NL (median CCI 3)  | 0–2 (42/26 0–1/2) | NR               | NR               | 90%        |
| Song et al    | Retrospective| ≥70                      | Double (TP)   | 60            | NL (median CCI 2)  | 0–2 (22/12 0–1/2) | NR               | NR               | 90%        |
| Song et al    | Retrospective| ≥70                      | Single (erlotinib) | 60            | NL (median CCI 2)  | 0–2 (20/14 0–1/2) | NR               | NR               | 90%        |
| Zhao et al    | Retrospective| ≥70                      | Double (DDP + S-1/Cape) | 61.6          | NL                  | 0–1 (0–1/2–3)    | NR               | NR               | 90%        |
| Song et al    | Retrospective| ≥70                      | Single (nimotuzumab) | NR            | NR                  | 0–2 (23/1 0–1/2) | NR               | NR               | 90%        |
| Lu et al      | Retrospective| ≥70 (70–86)              | Single (PF)   | 50.7          | NL                  | 0–3 (0–1/2–3)    | NR               | NR               | 90%        |
| Uno et al     | Retrospective| ≥70 (75–85)              | Single/double | 60            | NL                  | 0–2 (20/2 0–1/2) | NR               | NR               | 90%        |
| Nallapareddy  | Retrospective| ≥70 (70–86)              | Double/double | 45–64.8       | NR                  | 0–2 (23/1 0–1/2) | NR               | NR               | 90%        |
| Kosugi et al  | Retrospective| ≥70 (75–85)              | Single/double | 54–60         | NR                  | 0–1 (30/10 0–1/2) | NR               | NR               | 90%        |
| Xing et al    | Retrospective| ≥65                      | Double (DDP + Cape) | 51            | NL                  | 1–2 (54/3 1/2)   | NR               | NR               | 90%        |
scores <3 and <4. Among the 24 retrospective studies, 8 studies did not mention any information regarding the comorbidities of their enrolled patients. On the contrary, seven retrospective reports indicated the median CCI/ACCI clearly, with three publications reporting a median CCI of 2.

Nutrition
Malnutrition would certainly increase the risk of antitumor therapy and influence clinical outcomes, especially for elderly EC patients. In our systematic review, we found that the two prospective trials by Servagi-Vernat et al had criteria excluding patients with weight loss of more than 15% from baseline. In another Phase II trial conducted by Ji et al,10 weight loss was not used as an exclusion criterion, but over half of the patients (17/30, 56.7%) had <10% weight loss over nearly 6 months. Fourteen of the 24 retrospective studies did not reveal any results related to nutrition. The remaining 10 retrospective studies did not restrict the inclusion criteria in terms of malnutrition, with the main proportion of weight loss ranging from 0% to <10%.

Treatment compliance and severe toxicity
Different chemoradiation therapies could result in variable treatment compliance. In our systematic review, a total of 16 studies detailed the wide range of treatment compliance in elderly EC patients. The compliance rates ranged from 38.5% to 100%. Single-agent chemotherapy or targeted therapy had relatively higher treatment compliance rates (70.6%–100.0%) than did double-agent chemotherapies (38.5%–95.0%). The results of grade 3 or higher acute treatment-related toxicities are also presented in Table S2. Leukopenia was the most common acute toxicity reported in the literature, with incidences ranging from 0% to 72.7%. Ten studies also reported the incidence of severe neutropenia, ranging from 0% to 53.6%. The incidences of two other hematologic toxicities, anemia, and thrombocytopenia were 0%–45.5% and 0%–50.0%, respectively. Esophagitis was the most common radiation-related acute toxicity for elderly EC patients, ranging from 0% to 39.3%. Nausea/vomiting was the second most common during the acute phase. Other acute toxicities (grade >3) were rare with moderate tolerance.

Registered clinical trials
Nine registered clinical trials were found in the WHO and NIH registry network, based on our research methods (Table 2). Among these ongoing studies, six trials distributed across the mainland People’s Republic of China. Trial NCT 02735057, conducted in France, was the only study that
### Table 2 Registered clinical trials in the network

| ID                  | Country                          | Treatment protocol | Age          | Demographic data and social support | Comorbidity | Functional status (ECOG PS) | Cognition | Psychological | Nutrition | Polypharmacy | Geriatric syndromes | Note                  |
|---------------------|----------------------------------|--------------------|--------------|-------------------------------------|-------------|-----------------------------|-----------|---------------|-----------|--------------|---------------------|------------------------|
| ChiCTR-OIC-17011436 | People's Republic of China       | Lobaplatin + RT    | ≥65          | NR                                  | Strict      | 0–2                         | M         | NR            | Weight loss ≤ 10% | M                     | NR                    |                        |
| UMIN000020397       | Japan                            | PTX + RT           | 70≤ age ≤ 80 | NR                                  | Strict      | 0–2                         | NR        | M             | M                     | M                     | NR                    |                        |
| UMIN000001846       | Japan                            | Docetaxel + RT     | 70≤ age ≤ 80 | NR                                  | M           | 0–1                         | NR        | M             | M                     | M                     | NR                    |                        |
| NCT02716688         | People's Republic of China       | S-I + RT           | ≥70          | NR                                  | Strict      | 0–1                         | NR        | NR            | NR                    | NR                    | NR                    |                        |
| NCT02813967         | People's Republic of China       | S-I + RT           | 70≤ age ≤ 85 | NR                                  | Strict      | 0–1                         | NR        | NR            | NR                    | NR                    | NR                    |                        |
| NCT02375581         | People's Republic of China       | EGFR-TKI + RT      | 70≤ age ≤ 85 | NR                                  | Strict      | 0–2                         | M         | NR            | NR                    | NR                    | NR                    |                        |
| NCT02979691         | People's Republic of China       | S-I + RT           | ≥70          | NR                                  | Strict and CCI = 3 | 0–2 | NR           | NR                    | NR                    | NR                    | GA as end point         |
| NCT02606916         | People's Republic of China       | S-I + DDP + RT     | 70≤ age ≤ 80 | NR                                  | Strict and CCI = 4 | 0–2 | M            | M                     | Weight loss ≤ 15% | NR                    |                        |
| NCT02735057         | France                           | Cab + PTX + RT     | 75≤ age ≤ 80 | M                                   | Strict and CCI = 3 | 0–2 | M            | M                     | Weight loss ≤ 15% | NR                    | Pre-GA                 |
|                     |                                  |                    |              |                                     |              |                             |           |               |           |              |                     |                        |

**Abbreviations:** Cape, capecitabine; CCI, Charlson Comorbidity Index; DDP, cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; GA, geriatric assessment; M, moderate; NR, not reported; PTX, paclitaxel; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
detailed their study protocol in another journal. Among the
nine studies, chronological age, comorbidity, and functional
status were commonly established as notable markers for
the assessment of the elderly. To our surprise, the inclusion
criteria of malnutrition was only strictly restricted in three
studies. Other meaningful markers such as “cognitive status,”
“polypharmacy,” and “geriatric syndromes” were sporadi-
cally mentioned in these studies.

Discussion
Currently, high quality data from older adults with EC treated
with dCRT are extremely limited, according to our systematic
review. In the largest retrospective study to date, involving
patients over 70 years of age diagnosed with esophageal
cancer, Vlacich et al showed that over 37.1% of elderly
patients received dCRT and had a satisfactory median overall
survival (OS) time of 14.0 months (95% CI: 13.5–14.5). By
contrast, for elderly patients treated with trimodality ther-
apy, the median OS time was only increased to 19.3 months
(95% CI: 17.1–21.5) with the added sacrifice of abnormal
esophageal function that had an equally important impact on
psychological and geriatric syndromes. Using multivariate
logistic regression, they found that age over 80 years (odds
ratio: 0.79) was a strong indicator of decreased OS likeli-
hood and that patients with clinical stage III, tumors in the
upper and middle third of the esophagus, a Charlson–Deyo
comorbidity score <1, adenocarcinoma histology, and being
treated at a non-academic cancer center were more likely to
receive esophagectomy in the USA. Another large sample
retrospective analysis from the National Cancer Database
provided the opportunity to review treatment utilization
and outcomes in patients ≥80 years of age diagnosed with
stage I esophageal cancer. Their analysis revealed that 22%
of elderly patients received dCRT among the 923 patients.
The survival curve demonstrated a remarkable benefit over
observation alone (5-year OS: 20% vs 7%, P<0.001) with
the acceptable toxicity profile of dCRT.

Apart from known factors that are often associated with
treatment disparities such as socioeconomic status and
chronologic age, the functional and nutritional status at
diagnosis influenced treatment utilization. In 2010, Tougeron
et al investigated the baseline parameters that influenced
both therapeutic decisions and outcomes in 282 elderly EC
patients. Their outcomes further suggested that elderly EC
patients with good performance status, good nutritional sta-
tus, and without serious comorbidities were able to benefit
from curative treatment without severe adverse events.
In addition to functional and nutritional status for the elderly
patients, items of psychology and polypharmacy also play
an important role in treatment decisions. In a randomized
controlled study evaluating the psychological nursing inter-
ventions on personality characteristics and quality of life of
EC patients, Cheng et al proved that a psychological nurs-
ing intervention could affect the personality characteristics
of EC patients and improve quality of life. Furthermore,
analyses from elderly Danish cancer patients (including
EC patients) showed that newly diagnosed elderly cancer
patients (≥70 years) use more drugs than control patients
(odds ratio: 1.76). Drug use increased markedly in the last
6 months prior to cancer diagnosis. This finding suggested
an increased symptom burden in elderly patients and might
serve as a warning signal for general practitioners.

In general, elderly EC patients were at increased risk of
severe treatment-related toxicities and had a lower incidence
of treatment compliance than younger patients. Based on
the current review, compliance rates ranged from 38.5% to
100%. Single-agent chemotherapy or targeted therapy seemed
to have higher treatment compliance (70.6%–100.0%) than
did double-agent chemotherapies (38.5%–95.0%). Unlike
combined therapies for non-age-selected patients, our recent
Phase III trial demonstrated that dCRT (TP regimen and
radiation therapy) with erlotinib could achieve significantly
better OS and locoregional control than standard dCRT in
patients with inoperable ESCC. Furthermore, this trial con-
ﬁrmed that, aside from rash and radiation esophagitis, the
incidence of grade 3 or greater toxicities were manageable
and did not differ across the four groups. Traditionally, it
was thought that elderly patients have fewer body function
reserves, shorter life expectancy, and more need for socio-
economic support than young patients. Therefore, this finding
suggests that aggressive treatment decisions might not be
suitable for this unique and challenging subpopulation. In a
small-sample retrospective analysis, Wang et al observed
a signiﬁcantly higher incidence of severe leukocytopenia
in ESCC patients aged ≥75 than in patients aged between
70 and 75 years (41.9% vs 72.0%, respectively, P=0.024).
Hence, a detailed and full pretreatment evaluation, especially
containing GA-related domains should be routinely applied
to select appropriate elderly patients to receive dCRT.

Conclusion
Our systematic review fully demonstrates that the current
experience of receiving dCRT in elderly patients is based
on the results of a series of retrospective studies. High-level
evidence of RCTs remains lacking. Ongoing prospective
clinical trials should take GA-related domains into routine
consideration to select appropriate care for patients in the future. Survival benefits and the toxicity profiles should also be balanced among these treatment strategies.

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### Table S1 Baseline characteristics of the published reports in elderly EC patients who received dCRT or concurrent radiation with targeted therapy (full version)

| Study          | Study design | Histology (SCC/AC/other) | Age (range) | CT                      | Radiation dose (Gy) | Demographic data and social support | Comorbidity | Functional status (ECOG PS) |
|----------------|--------------|--------------------------|-------------|-------------------------|---------------------|-------------------------------------|-------------|-----------------------------|
| Servagi-Vernat et al<sup>1</sup> | Prospective | 19/11/0 | ≥75 (79.4–92) | Single (DDP/OHP) | 50 | NR | CCI ≤3 | 0–2 (23/7 0–1/2) and IADL |
| Servagi-Vernat et al<sup>2</sup> | Prospective | 15/7/0 | ≥75 (75–89) | Single (DDP) | 50 | NR | CCI ≤4 | 0–2 (16/6 0–1/2) |
| Ji et al<sup>3</sup> | Prospective | 29/1/0 | ≥65 (65–80) | Single (S-1) | 50 | NR | NR | 0–2 (16/14 0–1/2) |
| Xu et al<sup>4</sup> | Prospective | 73/0/0 | ≥65 (65–89) | Single (gefitinib) | 50 | NR | NR | 0–2 (18/2 0–1/2) |
| Ohba et al<sup>5</sup> | Prospective | 15/1/0 | ≥70 (73–81) | Single (DTX) | 60 | NR | NR | 0–1 |
| Zhang et al<sup>6</sup> | Retrospective | 74/6/2 | ≥70 (70–89) | Double (TP/PF) | 60 | NR | NL (median CCI 0) | 0–2 |
| Song et al<sup>7</sup> | Retrospective | 63/5/0 | ≥70 (70–88) | Single (S-1) | 54–60 | NR | NL (median CCI 3) | 0–2 (42/26 0–1/2) |
| Xu et al<sup>8</sup> | Retrospective | 36/76/0 | 65–79 | Double (S-FU + Tax) | 50.4 | NR | NL | 0–2 |
| Xu et al<sup>9</sup> | Retrospective | 16/40/0 | ≥80 (80–92) | Double (S-FU + Tax) | 50.4 | NR | NL | 0–2 |
| Song et al<sup>10</sup> | Retrospective | 31/3/0 | ≥70 | Double (TP) | 60 | NR | NL (median CCI 2) | 0–2 (22/12 0–1/2) |
| Song et al<sup>11</sup> | Retrospective | 31/3/0 | ≥70 | Single (erlotinib) | 60 | NR | NL (median CCI 2) | 0–2 (20/14 0–1/2) |
| Zhao et al<sup>12</sup> | Retrospective | 70/0/0 | ≥70 | Single (S-1/Cape) | 61.6 | NR | NL | 0–3 (63/7 0–1/2–3) |
| Zhao et al<sup>13</sup> | Retrospective | 16/0/0 | ≥70 | Double (DDP + S-1/Cape) | 61.6 | NR | NL | 0–1 |
| Münch et al<sup>14</sup> | Retrospective | 19/5/0 | ≥75 (78–85) | Single/double | 7–65 | NR | NL (median ACCI 7) | 0–2 (23/1 0–1/2) |
| Guo et al<sup>15</sup> | Retrospective | 16/0/0 | ≥70 (73–84) | Single (nimotuzumab) | NR | NR | NL | 0–2 (12/4 0–1/2) |
| Lu et al<sup>16</sup> | Retrospective | 188/0/0 | ≥75 (75–107) | Double (PF) | 50.7 | NR | NL | 0–3 |
| Uno et al<sup>17</sup> | Retrospective | 22/0/0 | ≥75 (75–85) | Single/double | ≥50, m 60 | NR | NL | 0–2 (20/2 0–1/2) |
| Nallapareddy et al<sup>18</sup> | Retrospective | 2/8/0 | ≥70 (70–86) | Single/double | 45–64.8 | NR | NR | NR |
| Kosugi et al<sup>19</sup> | Retrospective | 24/0/0 | ≥75 (75–85) | Single/double | 56–71, m 67 | NR | NR | NR |
| Xing et al<sup>20</sup> | Retrospective | 40/0/0 | ≥65 | Double (DDP + Cape) | 54–60 | NR | NR | 0–1 (30/10 0–1/2) |
| Go et al<sup>21</sup> | Retrospective | 57/0/0 | ≥65 (65–84) | Double (mPF) | 51 | NR | NL | 1–2 (54/3 1/2) |
| Takeuchi et al<sup>22</sup> | Retrospective | 33/0/0 | ≥70 (71–79) | Double (PF) | 60 | NR | NL | 0–1 |
| Wakui et al<sup>23</sup> | Retrospective | 22/0/0 | ≥75 (75–85) | Double (platinum +5-FU) | 50.4 | NR | NL | 0–2 |
| Li et al<sup>24</sup> | Retrospective | 32/0/0 | ≥70 (70–90) | Single/double | 50–60 | NR | NL | 0–2 |
| Hagiwara et al<sup>25</sup> | Retrospective | 38/0/0 | ≥75 (75–89) | Double (PF) | 60 | NR | NL | 0–1 |
| Tougeron et al<sup>26</sup> | Retrospective | 77/28/4 | ≥70 (70–88) | Double (PF/DDP + Irino) | 49 | NR | NL (median CCI 1) | 0–2 (87/22 0–1/2) |
| Uno et al<sup>27</sup> | Retrospective | 7/0/0 | ≥80 (80–85) | Single/double | 50–60 | NR | NR | 0–1 |
| Wang et al<sup>28</sup> | Retrospective | 56/0/0 | ≥70 (70–87) | Double (DDP + S-1) | 54 | NR | NR | 0–1 |
| Anderson et al<sup>29</sup> | Retrospective | 13/12/0 | ≥65 (66–88) | Double (5-FU + mitomycin) | 50.4 | NR | NL (median CCI 2) | 1–2 |
| Chen et al<sup>30</sup> | Retrospective | 49/0/0 | ≥65 | Double (DDP + Cape) | 56–59.4 | NR | NL | 0–2 (31/18 0–1/2) |
| Zhao et al<sup>31</sup> | Retrospective | 52/0/0 | ≥75 (75–90) | Double (PF) | 54–66 | NR | NL | 0–2 (46/6 0–1/2) |

(Continued)
| Study                        | Cognition                  | Nutrition                | Psychological | Polypharmacy | Geriatric syndromes | Compliance |
|-----------------------------|----------------------------|--------------------------|---------------|--------------|--------------------|------------|
| Servagi-Vernat et al.       | Folstein’s test            | Weight loss ≤15%         | NR            | NR           | NR                 | 93.30%     |
| Servagi-Vernat et al.       | NR                         | Weight loss ≤15%         | NR            | NR           | NR                 | 100%       |
| Ji et al.                   | NR                         | NL (main <10%)           | NR            | NR           | NR                 | 89.00%     |
| Xu et al.                   | NR                         | NR                       | NR            | NR           | NR                 | 90%        |
| Ohba et al.                 | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Zhang et al.                | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Song et al.                 | NR                         | NL (main <10%)           | NR            | NR           | NR                 | 67.10%     |
| Lv et al.                   | NR                         | NL (main <10%)           | NR            | NR           | NR                 | 70.60%     |
| Xu et al.                   | NR                         | NR                       | NR            | NR           | NR                 | 95%        |
| Xu et al.                   | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Song et al.                 | NR                         | NL (main <10%)           | NR            | NR           | NR                 | NR         |
| Song et al.                 | NR                         | NL (main <10%)           | NR            | NR           | NR                 | NR         |
| Zhao et al.                 | NR                         | NL (main <5%)            | NR            | NR           | NR                 | NR         |
| Zhao et al.                 | NR                         | NL (main <5%)            | NR            | NR           | NR                 | NR         |
| Münch et al.                | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Guo et al.                  | NR                         | NR                       | NR            | NR           | NR                 | 100%       |
| Lu et al.                   | NR                         | NR                       | NR            | NR           | NR                 | 52.70%     |
| Uno et al.                  | NR                         | NR                       | NR            | NR           | NR                 | 86.40%     |
| Nallapareddy et al.         | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Kosugi et al.               | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Xing et al.                 | NR                         | NL (main ≥5%)            | NR            | NR           | NR                 | NR         |
| Go et al.                   | NR                         | NR                       | NR            | NR           | NR                 | 75.40%     |
| Takeuchi et al.             | NR                         | NR                       | NR            | NR           | NR                 | 66.70%     |
| Wakui et al.                | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Li et al.                   | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Hagiwara et al.             | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Togheron et al.             | NR                         | NL (main <10%)           | NR            | NR           | NR                 | 38.50%     |
| Uno et al.                  | NR                         | NR                       | NR            | NR           | NR                 | NR         |
| Wang et al.                 | NR                         | NL (main ≤10%)           | NR            | NR           | NR                 | 67.90%     |
| Anderson et al.             | NL (main 5–30 lb)          | NR                       | NR            | NR           | NR                 | 88.00%     |
| Chen et al.                 | NL (main <5%)              | NR                       | NR            | NR           | NR                 | NR         |
| Zhao et al.                 | NL (main >0%)              | NR                       | NR            | NR           | NR                 | NR         |

**Note:** TP, paclitaxel and DDP; PF, 5-FU and DDP.

**Abbreviations:** 5-FU, 5-fluorouracil; AC, adenocarcinoma; Cape, capecitabine; CCI, Charlson Comorbidity Index; CT, chemotherapy; dCRT, definitive chemoradiotherapy; DDP, cisplatin; DTX, paclitaxel; mPF, modified 5-Fu and DDP; EC, esophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; Irino, irinotecan; NL, not limited; NR, not reported; OHP, oxaliplatin; Ref, reference; SCC, squamous cell carcinoma; Tax, taxotere.
Table S2 Toxicity profile reported in the literature

| Study               | Number | Leukocytopenia | Neutropenia | Anemia | Thrombopenia | Dysphagia | Esophagitis | Nausea/ vomiting | Mucositis | Pneumonitis | Diarrhea | Fatigue | Death |
|---------------------|--------|----------------|-------------|--------|--------------|-----------|-------------|-------------------|-----------|-------------|----------|---------|-------|
| Servagivernat et al | 30     | 0              | 0           | 1      | 0            | 0         | 0           | 0                 | 12        | 0           | 0        | 0       | 0     |
| Ji et al            | 30     | 4              | 3           | 1      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Xu et al           | 16     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Zhong et al        | 57     | 2              | 2           | 1      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Song et al         | 34     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Uno et al          | 16     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Wang et al         | 20     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Manshadi et al     | 30     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Ahuja et al        | 22     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Nakashima et al    | 12     | 2              | 2           | 1      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Song et al         | 34     | 2              | 2           | 1      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Ohba et al         | 16     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Zhang et al        | 73     | 6              | 6           | 5      | 3            | 4         | 4           | 4                 | 2         | 0           | 0        | 0       | 0     |
| Xu et al           | 82     | 1              | 1           | 1      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Song et al         | 112    | 3              | 3           | 3      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Xu et al           | 68     | 5              | 5           | 5      | 3            | 4         | 4           | 4                 | 2         | 0           | 0        | 0       | 0     |
| Song et al         | 56     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Song et al         | 34     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Song et al         | 24     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Song et al         | 16     | 2              | 2           | 1      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Uno et al          | 22     | 2              | 2           | 1      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Takeuchi et al     | 33     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Xing et al         | 22     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Koseki et al       | 40     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Kong et al         | 57     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Go et al           | 34     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Go et al           | 12     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Takeuchi et al     | 33     | 2              | 2           | 1      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Waki et al         | 22     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Hagiwara et al     | 38     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Wang et al         | 56     | 2              | 2           | 1      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Anderson et al     | 25     | 3              | 3           | 3      | 5            | 6         | 2           | 2                 | 2         | 0           | 0        | 0       | 0     |
| Chen et al         | 49     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
| Zhang et al        | 52     | 0              | 0           | 0      | 0            | 0         | 0           | 0                 | 0         | 0           | 0        | 0       | 0     |
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