Introduction

Gastric and esophageal cancer are the 5th and 7th most common cancers worldwide and the incidence of esophageal cancer is rapidly rising [1]. Approximately 30–50 % of patients with esophagogastric cancer (i.e. esophageal or gastric cancer) have metastatic disease at the time of initial diagnosis (i.e. synchronous) [2]. In addition, >30 % of patients develop metastatic disease during follow-up after initial primary tumor treatment with curative intent (i.e. metachronous) [3,4]. Patients with metastatic esophagogastric cancer have a poor prognosis.

**Abbreviations:** OS, Overall survival; OMD, Oligometastatic disease; SBRT, Stereotactic body radiotherapy; NCR, Netherlands Cancer Registry; RCT, Randomized controlled trial; HR, Hazard ratio; SD, Standard deviation; IQR, Interquartile range.

* Corresponding author at: Department of Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.

1 Shared first author.

https://doi.org/10.1016/j.ctro.2022.08.012

Received 28 March 2022; Received in revised form 16 August 2022; Accepted 19 August 2022

Available online 24 August 2022
with a median overall survival (OS) between 3 and 9 months [4-6], and are usually treated with systemic therapy or best supportive care [7-10].

In a small portion of metastatic patients, distant metastases are limited in number and distribution, so-called oligometastatic disease (OMD) [11]. OMD reflects a disease state between locoregional and widespread metastatic disease [11]. Randomized controlled trials (RCTs) have shown that local treatment (e.g. metastasectomy or stereotactic body radiotherapy [SBRT]) improves OS as compared with systemic therapy alone in patients with breast, prostate, colorectal, or lung cancer [12,13]. For esophagogastric cancer, phase II trials have suggested improved OS after local treatment of OMD [14,15], which is currently being investigated in RCTs [16-18].

However, the applicability and generalizability of the currently available data from the literature is unclear since clinical trial results cannot always be reproduced in the real-world setting due to strict selection criteria [19]. Therefore, real-world population-based data are a valuable addition to trial results because they deepen the understanding of the outcome of therapies in patients encountered on a day-to-day basis, making results better interpretable in clinical practice [20]. Furthermore, population-based studies enable us to analyze a relatively large population considering the proportion of patients receiving local treatment for OMD is relatively small [21]. Finally, the adoption of local treatment of OMD varies and knowledge on outcomes on a population-based level is currently lacking. Therefore, this study aimed to determine OS and independent prognostic factors for OS after local treatment or systemic therapy for OMD in patients with esophagogastric cancer on a nationwide population-based level.

Methods and materials

Study design

This study included patients registered in the Netherlands Cancer Registry (NCR). The NCR is the only national oncological registry in The Netherlands and provides cancer statistics among all 17.4 million residents. According to the Central Committee on Research involving Human Subjects, this study did not need approval by an institutional review board in The Netherlands. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry and the scientific committee of the Dutch Upper GI Cancer Group (DUCG). The study was reported according to the guidelines of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Supplementary A) [22].

Patient inclusion

Consecutive patients with synchronous or metachronous metastatic esophagogastric cancer were identified from the NCR between 2015 and 2016 (i.e. according to UICC/AJCC 7th edition [18] as Tx-4b, Nx-N3, M1 esophagogastric cancer were identified from the NCR between 2015 and 2016). OMD reflects a disease state between locoregional and widespread metastatic disease [11]. Randomized controlled trials (RCTs) have shown that local treatment (e.g. metastasectomy or stereotactic body radiotherapy [SBRT]) improves OS as compared with systemic therapy alone in patients with breast, prostate, colorectal, or lung cancer [12,13]. For esophagogastric cancer, phase II trials have suggested improved OS after local treatment of OMD [14,15], which is currently being investigated in RCTs [16-18].

However, the applicability and generalizability of the currently available data from the literature is unclear since clinical trial results cannot always be reproduced in the real-world setting due to strict selection criteria [19]. Therefore, real-world population-based data are a valuable addition to trial results because they deepen the understanding of the outcome of therapies in patients encountered on a day-to-day basis, making results better interpretable in clinical practice [20]. Furthermore, population-based studies enable us to analyze a relatively large population considering the proportion of patients receiving local treatment for OMD is relatively small [21]. Finally, the adoption of local treatment of OMD varies and knowledge on outcomes on a population-based level is currently lacking. Therefore, this study aimed to determine OS and independent prognostic factors for OS after local treatment or systemic therapy for OMD in patients with esophagogastric cancer on a nationwide population-based level.

Methods and materials

Study design

This study included patients registered in the Netherlands Cancer Registry (NCR). The NCR is the only national oncological registry in The Netherlands and provides cancer statistics among all 17.4 million residents. According to the Central Committee on Research involving Human Subjects, this study did not need approval by an institutional review board in The Netherlands. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry and the scientific committee of the Dutch Upper GI Cancer Group (DUCG). The study was reported according to the guidelines of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Supplementary A) [22].

Patient inclusion

Consecutive patients with synchronous or metachronous metastatic esophagogastric cancer were identified from the NCR between 2015 and 2016 (i.e. according to UICC/AJCC 7th edition [18] as Tx-4b, Nx-N3, M1 and according to ICD-10 [23] as 15.3–15.5, 15.8, 15.9, and 16.0–16.9). The years 2015 and 2016 were selected because the NCR registered additional data on metastatic metastases for these years only. OMD was defined as distant metastases in 1 organ or 1 extra-regional lymph node region comparable with a recent systemic review on definitions of oligometastatic esophagogastric cancer in current literature [24]. OMD was not defined by a maximum number of lesions per organ/extra-regional lymph node region because this was not recorded by the NCR. Patients undergoing local treatment of OMD (i.e. SBRT or metastasectomy) or systemic therapy were included. SBRT was defined as radiotherapy according to one of the following radiotherapy schemes: ≥10 Gy per fraction with ≥1 fraction, ≥5 Gy per fraction with <12 fractions, or ≥7 Gy per fraction with ≤5 fractions. All other radiotherapy schemes were considered palliative radiotherapy. Patients undergoing palliative radiotherapy were not included. Metastasectomy was defined as surgery, which could include radiofrequency ablation.
for Windows, version 3.6.3. A two-sided p-value < 0.05 was considered statistically significant.

**Results**

Between 2015 and 2016, 4265 patients with synchronous or metachronous metastatic esophagogastric cancer were identified from the NCR, of whom 594 patients who underwent local treatment or systemic therapy for OMD were included. First, the 105 patients undergoing local treatment for OMD with or without systemic therapy will be described. Subsequently, the 489 patients undergoing systemic therapy alone for OMD (Fig. 1).

The 105 included patients were generally male (71%) with a mean age of 64 years (SD: ±8) and mostly had a WHO performance score of 0–1 at the time of treatment (62%). The primary tumors were predominantly adenocarcinomas (80%) located in the distal third of the esophagus (57%). The predominant clinical tumor stage was cT3 (66%) and nodal stage cN1 (45%). For patients who underwent primary tumor resection (n = 74), the predominant pathological tumor stage was pT3 (45%) and nodal stage pN0 (45%).

Most patients had metachronous OMD (62%, i.e. OMD detected after primary tumor treatment). OMD was located in 1 distant organ (79%), 1 extra-regional lymph node region (12%), or the peritoneum (9%). The median disease-free interval for metachronous OMD was 17 months (IQR: 14–24) after diagnosis of the primary tumor. OMD was confirmed with pathological assessment (71%) or repeated follow-up imaging (29% Table 1).

Primary tumor treatment consisted of surgery in 74 patients (71%), definitive chemoradiotherapy in 12 patients (12%), or no primary tumor treatment in 19 patients (17%). Treatment of OMD consisted of local treatment alone in 83 patients (79%), including SBRT alone in 34 patients (33%), metastasectomy alone in 35 patients (32%), or both metastasectomy and SBRT in 14 patients (14%). Local treatment of OMD was combined with systemic therapy in 22 patients (21%), including metastasectomy plus systemic therapy in 14 patients (14%), SBRT plus systemic therapy in 7 patients (7%), or both metastasectomy and SBRT plus systemic therapy in 1 patient (1%). Systemic therapy was predominantly administrated before local treatment of OMD (73%) and generally consisted of 2 chemotherapy agents (68%). The most common chemotherapy regimen consisted of capecitabine and oxaliplatin (36%, Table 2).

A total of 64 patients underwent metastasectomy. Metastasectomy was more commonly applied than SBRT for OMD in the liver (80%), the extra-regional lymph nodes (67%), or the peritoneum (100%). A total of 56 patients underwent SBRT. Applied SBRT schedules are provided in Supplementary File B. SBRT was more often performed than metastasectomy for OMD in the lung (73%) or bone (75%). Local treatment of OMD plus systemic therapy was common in patients with OMD in the liver (50%) or peritoneum (78%, Supplementary File C).

Patients with synchronous as compared with metachronous OMD less often underwent primary tumor resection (47% versus 87%), more often underwent local treatment of OMD plus systemic therapy (37% versus 10%), and had extra-regional lymph node oligometastases (19% versus 2%). Patients with metachronous as compared with synchronous

| Table 1 | Patient and tumor characteristics of included patients. |
|---------|------------------------------------------------------|
| **Factor** | **Local +/- systemic therapy** (n = 105) | **Systemic therapy only** (n = 489) | **P-value** |
| Mean age in years (±SD) | 64 (±8) | 64 (±10) | 0.894 |
| **Sex** | | | 0.460 |
| Male | 75 (71 %) | 369 (75 %) | |
| Female | 30 (29 %) | 120 (25 %) | |
| **WHO performance score** | | <0.001 | |
| 0 | 35 (33 %) | 119 (24 %) | |
| 1 | 27 (29 %) | 165 (34 %) | |
| >1 | 6 (5 %) | 53 (11 %) | |
| Missing | 37 (33 %) | 152 (31 %) | |
| **Location of the primary tumor** | | <0.001 | |
| Upper or middle third esophagus | 14 (13 %) | 51 (10 %) | |
| Lower third esophagus | 60 (57 %) | 187 (38 %) | |
| Esophageal junction/cardia | 2 (2 %) | 14 (3 %) | |
| Gastroesophageal junction/cardia | 13 (12 %) | 80 (16 %) | |
| Stomach | 16 (15 %) | 157 (32 %) | |
| **Clinical tumor stage** | | <0.001 | |
| cT1b or cT2 | 25 (24 %) | 169 (35 %) | |
| cT3 or cT4 | 74 (70 %) | 168 (35 %) | |
| Missing | 5 (5 %) | 102 (21 %) | |
| **Pathological tumor stage** | | 0.349 | |
| pT0 | 12 (16 %) | 8 (9 %) | |
| pT1 or pT2 | 25 (33 %) | 37 (42 %) | |
| pT3 or pT4 | 36 (48 %) | 42 (47 %) | |
| Missing | 1 (1 %) | 2 (2 %) | |
| **Pathological nodal stage** | | 0.747 | |
| pN0 | 33 (44 %) | 34 (38 %) | |
| pN1 | 19 (26 %) | 22 (25 %) | |
| pN2 or pN3 | 21 (28 %) | 22 (25 %) | |
| Missing | 1 (1 %) | 11 (12 %) | |
| **Histology of the primary tumor** | | 0.459 | |
| Adenocarcinoma | 84 (80 %) | 407 (84 %) | |
| Squamous cell carcinoma | 21 (20 %) | 80 (16 %) | |
| **Signet ring cell carcinoma** | | 0.695 | |
| **Differentiation grade** | | <0.001 | |
| Good-moderate | 40 (38 %) | 114 (23 %) | |
| Poor/undifferentiated | 46 (44 %) | 187 (38 %) | |
| Missing | 19 (18 %) | 188 (38 %) | |
| **Timing of detection** | | <0.001 | |
| Synchronous | 43 (41 %) | 372 (77 %) | |
| Metachronous | 62 (59 %) | 114 (23 %) | |
| **Median disease-free interval [IQR]** | 17 [14, 24] | 18 [15, 27] | 0.546 |
| **Location of OMD** | | <0.001 | |

(continued on next page)
OMD more often underwent local treatment of OMD alone (90% versus 63%) and had brain oligometastases (45% versus 9%, Supplementary File D).

A total of 489 patients who underwent systemic therapy alone for OMD. Patients who underwent systemic therapy alone for OMD more often had gastric cancer (32% versus 15%, p < 0.001), synchronous OMD (77% versus 41%, p < 0.001), liver metastases (37% versus 10%, p < 0.001), and an uncontrolled primary tumor (63% versus 18%, p < 0.001) as compared with patients who underwent local treatment for OMD with or without systemic therapy (Table 1 and Table 2).

The median follow-up time for patients undergoing local treatment for OMD with or without systemic therapy was 49.8 months (IQR: 37.2-55.0) and for patients undergoing systemic therapy alone was 59.0 months (IQR: 50.0-62.0). The median OS after local treatment of OMD plus systemic therapy was 22.7 months (95% CI: 14.7-42.6), versus 16.0 months (95% CI: 12.7-21.8) after local treatment of OMD alone, and 8.5 months (95% CI: 7.9-9.6) after systemic therapy alone (Fig. 2).

In multivariable analysis (Table 3), worse OS was independently associated with worse WHO performance scores (HR 1.41, 95% CI: 1.32-1.75; Supplementary File E), poorly or undifferentiated tumor as compared with a good or moderately differentiated tumor (HR 1.37, 95% CI: 1.06-1.76; Supplementary File F), and peritoneal as compared with extra-regional lymph node metastases (HR 1.39, 95% CI: 1.00-1.93; Supplementary File G).

Improved OS was independently associated with local treatment of OMD alone or combined with systemic therapy as compared with systemic therapy alone (HR 0.52, 95% CI: 0.31-0.90 and HR 0.42, 95% CI: 0.22-0.82, respectively), and a controlled primary tumor versus uncontrolled primary tumor (HR 0.48, 95% CI: 0.27-0.86; Supplementary File H).

Discussion

This nationwide population-based cohort suggests that local treatment of OMD alone or combined with systemic therapy can be a preferred treatment approach for patients with oligometastatic esophageal cancer since this treatment approach was independently associated with improved OS as compared with systemic therapy of OMD alone (median OS of 16.0 months or 22.7 months versus 8.5 months). However, these results must be interpreted with care because selection may have resulted in a potential overestimation of OS after local treatment of OMD because patients with favorable patient- and tumor characteristics were more often selected for treatment (i.e. confounding by indication) [33]. In addition, the NCR did not record the number or size of OMD lesions which may have impacted on OS [27]. Therefore, randomized controlled trials are warranted to confirm our findings by indication [33].
The benefit of local treatment of OMD plus systemic therapy over systemic therapy alone has been previously suggested by a phase II non-randomized trial by Al-Batran et al. [14]. This study included patients with gastric or gastroesophageal junction adenocarcinoma with synchronous OMD. Patients who responded to fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy underwent resection of the primary tumor and metastases [14]. This study showed improved OS after resection of the primary tumor and metastases in patients who responded to FLOT chemotherapy as compared with patients who did not respond to systemic therapy (median OS of 31.3 months versus 15.9 months, respectively) [14]. These results have resulted in an ongoing phase III RENAISSANCE trial in which patients with gastric or gastro-esophageal junction adenocarcinoma with synchronous OMD who respond to FLOT chemotherapy will be randomized to either continuation of FLOT chemotherapy or resection of the primary tumor and metastases [16]. In addition, the results of our study are comparable with the phase II trial by Liu et al. [15]. This study included patients with esophageal squamous cell carcinoma with metastatic OMD who underwent SBRT and 50% received adjuvant systemic therapy [15]. This study showed an OS of 24.6 months [15].

Although several non-randomized studies have suggested excellent OS in patients undergoing local treatment of OMD plus systemic therapy [14,15], this study shows that only 21% of patients undergoing local treatment received combined systemic therapy as compared with 100% [14] and 50% [15] in these phase II trials. The limited use of combined local treatment plus systemic therapy in our population-based study was mainly seen in patients with brain oligometastasis, which formed a relatively large proportion of our study population (30%). Chemotherapy has limited activity in the brain, which has been mainly attributed to the blood-brain barrier [34]. Patients with brain oligometastasis were excluded from these phase II trials [14,15]. Besides the high portion of patients with brain oligometastasis, the limited use of systemic therapy combined with local treatment of OMD might also be explained by the lack of evidence-based guidelines to guide treatment decision-making and the lack of completed RCTs in the setting of esophagogastroduodenal OMD.

In addition to the German RENAISSANCE trial, several phase III trials are currently investigating the benefit of local treatment for OMD plus systemic therapy over systemic therapy alone [16-18]. In the American ECOG study (NCT04248452), patients with synchronous or metachronous OMD limited to 3 metastases will be included [17]. Patients with response to chemotherapy will be randomized to either SBRT plus continuation of chemotherapy or continuation of chemotherapy alone [17]. Finally, in the French SURGIGAST trial (NCT03042169), patients with synchronous gastric cancer with synchronous OMD limited to the retroperitoneal lymph nodes and/or 1 organ with metastases will be included [18]. Patients with response to “standard chemotherapy” will be randomized to either resection of the primary tumor and oligometastases or continuation of chemotherapy [18].

However, none of these studies have incorporated immunotherapy in the treatment algorithm for OMD, although several studies have shown improved survival outcomes for patients with esophagogastroduodenal cancer treated with immunotherapy in the first-line palliative setting [35] or in the adjuvant setting after a pathological incomplete response after neoadjuvant chemoradiotherapy and surgery [36]. Currently, it is unknown if immunotherapy also improves survival outcomes in the OMD setting before and/or after local treatment for OMD in patients with esophagogastroduodenal cancer. Therefore, a potential future study could assess the benefit of immunotherapy plus local treatment for OMD in patients with esophagogastroduodenal cancer.

Certain limitations apply to this study that warrants caution for the interpretation of results. First, no additional prognostic factors could be
Table 3 (continued)

| Primary tumor controlled | N= | Univariable | Multivariable |
|--------------------------|----|-------------|---------------|
|                         |    | HR (95% CI) | p-value       | HR (95% CI)   | p-value       |
| No                      | 505 | Reference   | ref           | Reference     | ref           |
|                         | 86  | (0.44–1.36) | (0.27–0.86)   | (0.27–0.86)   |
| Treatment for OMD        |    |             |               |               |
| Systemic                 | 486 | Reference   | <0.001        | Reference     | <0.001        |
| Local                    | 83  | 0.32        | (0.24–0.41)   | 0.52          | (0.31–0.90)   |
| Local + Systemic         | 22  | 0.32        | (0.19–0.52)   | 0.42          | (0.22–0.82)   |

Conclusion

In conclusion, our results suggest that the preferred approach to oligometastatic esophagogastric cancer includes radical local treatment of OMD alone (e.g. metastasectomy or SBRT) or a combined approach consisting of radial local treatment of OMD plus systemic therapy (e.g. chemotherapy). However, our results are most likely biased. Therefore, randomized controlled trials are warranted to confirm these results.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. van Laarhoven reports consultant or advisory role: BMS, Dragonfly, Lilly, Merck, Nordic Pharma, Servier; research funding and/or medication supply: Bayer, BMS, Celgene, Janssen, Incyte, Lilly, Merck, Nordic Pharma, Philips, Roche, Servier; Dr. Verhoeven reports grants from Bristol-Myer Squibb and Roche, outside the submitted work; Dr. Haj Mohammad reports personal fees from BMS, Lilly, MSD, Servier, and Astra Zeneca, outside the submitted work; the other authors have nothing to disclose.
Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.08.012.

References

[1] Seng H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.

[2] Koemans WM, Luijten JGHB, van der Kaaij RT, Grootsholten C, Snaeboersjons P, Verhoeven RHA, et al. The metastatic pattern of intestinal and diffuse type gastric carcinoma – A Dutch national cohort study. Cancer Epidemiol 2020;69:101846. https://doi.org/10.1016/j.canep.2020.101846.

[3] Wu S-G, Zhang W-W, Sun J-Y-Y, Li F-Y, Lin Q, He Z-Y. Patterns of distant metastasis between histological types in esophageal cancer. Front Oncol 2018. https://doi.org/10.3389/fonc.2018.00302.

[4] Bernards N, Creemers GJ, Nieuwenhuijzen GAP, Boscha K, Pruijt JFM, Lemmens VEP. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy. Ann Oncol 2013;24:3056–60. https://doi.org/10.1093/annonc/mdt306.

[5] Parry K, Visser E, van Rossum PSN, Mohammad NH, Ruurda JP, van Hillegersberg R. Prognosis and treatment after diagnosis of recurrent esophageal carcinoma following esophagectomy with curative intent. Ann Surg Oncol 2015;22(53):1292–300. http://dx.doi.org/10.1245/s10434-015-4840-5.

[6] Bernards N, Haj Mohammad N, Creemers GJ, zoetema T, Roulkema JA. Nieuwenhuijzen GAP. Improvement in survival for patients with synchronous metastatic esophageal cancer in the south of the Netherlands from 1994 to 2013. Acta Oncol (Madrid) 2016;55(9-10):1161–7. https://doi.org/10.3322/caac.20161.1176249.

[7] Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v38–v60. https://doi.org/10.1093/annonc/mdw329.

[8] Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: The AIO-FLOT3 trial. JAMA Oncol 2017;3(9):1237. https://doi.org/10.1001/jamaoncol.2017.2016;17(7):1672–3. https://doi.org/10.1002/cncr.29940.

[9] Ajani JA, D’Antonio JA, Wiersema J, et al. Adjuvant chemotherapy for patients with stage IIIC gastric cancer with positive nodes: the NCCN Guidelines: Gastric cancer. Natl Compr Cancer Netw 2019.

[10] NCCN. NCCN Guidelines: Gastric cancer. Natl Compr Cancer Netw 2019;17(12):1672–3. https://doi.org/10.1002/cncr.317495.

[11] Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13(1):8–17. https://doi.org/10.1200/jco.1995.13.1.8.

[12] Al-Batran S-E, Goetze TO, Muehlbauer M, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical treatment (chemotherapy) for patients with esophageal and gastric cancer that has failed to respond to systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol 2016;17(10):1150–8. https://doi.org/10.1016/s1470-2045(16)30532-0.

[13] Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek CJ, et al. Stereotactic ablative radiotherapy versus standard care for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017;18(11):1421–9. https://doi.org/10.1016/s1470-2045(17)30356-9.

[14] ter Veer E, van Kleef J, Schokker S, van der Woude SO, Laarmann M, Haj Mohammad N, et al. Predictive and prognostic factors for overall survival and distant metastases in metastatic oesophagogastric cancer. A systematic review and meta-analysis. Eur J Cancer 2018;103:214–26. https://doi.org/10.1016/j.ejca.2018.07.132.

[15] Averitt AJ, Weng C, Ryan P, Perotte A. Translating evidence into practice: Partners in the evolution of medical evidence. Br J Cancer 2021;203:1–20. https://doi.org/10.1038/s41416-021-0358-z.

[16] Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: Partners in the evolution of medical evidence. Br J Cancer 2021;203:1–20. https://doi.org/10.1038/s41416-021-0358-z.

[17] ECOG-ACRIN Cancer Research. Testing the addition of radiotherapy to the usual treatment (chemotherapy) for patients with esophageal and gastric cancer that has spread to a limited number of other places in the body. clinicaltrials.gov. NCT04248452. 2020. doi:10.1515/1001-3878-24657-2020.

[18] ECOG-ACRIN Cancer Research. Testing the addition of radiotherapy to the usual treatment (chemotherapy) for patients with esophageal and gastric cancer that has spread to a limited number of other places in the body. clinicaltrials.gov. NCT03942169. Accessed July 11, 2019.