

Prognosis of Interval Distant Metastases After Neoadjuvant Chemoradiotherapy for Esophageal Cancer



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ABSTRACT

BACKGROUND In esophageal cancer patients, distant metastases develop between the start of neoadjuvant chemoradiotherapy and planned surgery, so-called interval metastases. The primary aim of this study was to assess management, overall survival (OS), and prognostic factors for OS in these patients. A secondary aim was to compare OS with synchronous metastatic patients.

METHODS Esophageal cancer patients with interval distant metastases were identified from the Netherlands Cancer Registry (2010 to 2017). Management was categorized into metastasis-directed therapy (MDT), primary tumor resection, or best supportive care (BSC). The OS was calculated from the diagnosis of the primary tumor. Prognostic factors affecting OS were studied using Cox proportional hazard models. Propensity score-matching (1:3) generated matched cases with synchronous distant metastases.

RESULTS In all, 208 patients with interval metastases were identified: in 87 patients (42%) MDT was initiated; in 10%, primary tumor resection only; in 7%, primary tumor resection plus MDT; and in 41%, BSC. Median OS was 10 months (interquartile range, 8.6 to 11.1). Compared with BSC, superior OS was independently associated with MDT (hazard ratio [HR] 0.36; 95% confidence interval [CI], 0.26 to 0.49), primary tumor resection (HR 0.55; 95% CI, 0.33 to 0.94), and primary tumor resection plus MDT (HR 0.20; 95% CI, 0.10 to 0.38). Worse OS was independently associated with signet ring cell carcinoma (HR 1.92; 95% CI, 1.12 to 3.28) and poor differentiation grade (HR 1.96; 95% CI, 1.35 to 2.83). The OS was comparable between matched patients with interval and synchronous distant metastases (10.2 versus 9.4 months, $P = .760$).

CONCLUSIONS In esophageal cancer patients treated with neoadjuvant chemoradiotherapy with interval distant metastases, the OS was poor and comparable to that of synchronous metastatic patients.

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Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is currently considered an important multimodality treatment option for patients with locally advanced esophageal or gastroesophageal junction cancer.¹⁻⁵ Perioperative chemotherapy is an alternative multimodality treatment option for locally advanced gastroesophageal junction adenocarcinoma.^{1,5-8} The overall survival (OS) of

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Abbreviations and Acronyms

CI = confidence interval
BSC = best supportive care
HR = hazard ratio
IQR = interquartile range
MDT = metastasis-directed therapy
NCR = Netherlands Cancer Registry
nCRT = neoadjuvant chemoradiotherapy
OS = overall survival

patients with locally advanced esophageal or gastroesophageal junction cancer treated with nCRT followed by surgery remains relatively poor with an estimated 5-year OS rate of 40% to 50%, predominantly due to distant recurrences.^{4,9}

Distant metastases may also appear at initial presentation (ie, synchronous metastases) or between the start of nCRT and planned surgery, so-called interval metastases.¹⁰ These distant metastases are labeled as “interval” distant metastases because they were not recognized during initial staging and were detected before completion of treatment with curative intent.^{10,11} Restaging with ¹⁸F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (¹⁸F-FDG PET/CT) imaging after nCRT—before surgery—detects interval distant metastases in approximately 8% of esophageal cancer patients.^{10,12-14}

Because evidence is scarce, the efficacy of different treatment strategies and prognostic factors for OS in patients with interval distant metastases are unknown. In addition, specific knowledge of the OS in comparison with patients with synchronous distant metastases is lacking. Therefore, the primary aims of this population-based cohort study was to assess management, OS, and prognostic factors for OS of patients with interval distant metastases. A secondary aim was to compare the OS with a matched group of patients with synchronous distant metastases.

PATIENTS AND METHODS

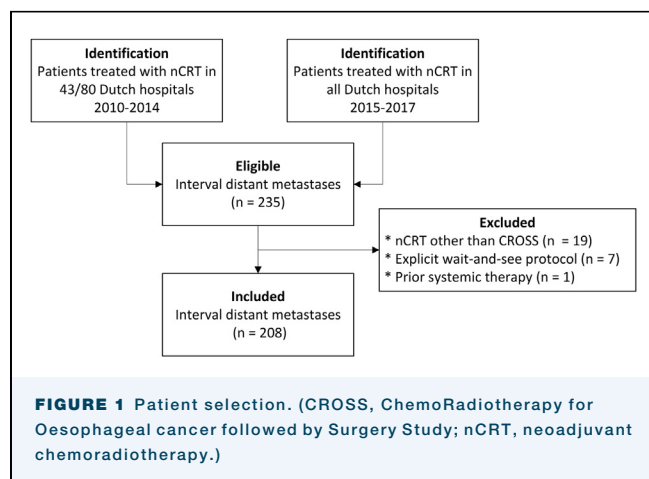
STUDY DESIGN AND POPULATION. This population-based cohort study included patients with interval distant metastases registered in the Netherlands Cancer Registry (NCR) between 2015 and 2017. The NCR captures new cancer incidences among all 17.4 million residents in the Netherlands. In addition, because the NCR did not routinely record interval distant metastases between 2010 and 2014, for this specific research question additional data were collected by the NCR from a subset of 43 (of 80) Dutch hospitals. This subset can be considered a representative sample in terms of annual number of patients, type of hospital, and location in the Netherlands, and included all patients diagnosed in these hospitals between 2010

and 2014.¹⁵ Vital status is obtained through annual linkage with the municipal population registers, and was last updated on the first of February 2019. This study did not need approval by an Institutional Review Board in the Netherlands according to the Central Committee on Research Involving Human Subjects. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.¹⁶

PATIENT INCLUSION. Patients with newly diagnosed, locally advanced cancer (ie, according to TNM seventh edition¹⁷ cT1-4a, cN0-3, cM0) of the thoracic esophagus or gastroesophageal junction (ie, according to ICD-O version 3¹⁸ C15.3 to 15.5, C15.9, and C16.0) who received nCRT before a planned esophagectomy or gastrectomy were eligible for inclusion. Interval distant metastases were defined as distant metastases detected between 3 days after the start of nCRT and 120 days after completion of nCRT or detected during planned surgery. Distant metastases detected more than 120 days after completion of nCRT were not considered interval metastases because that was considered an unusually long time between completion of nCRT and elective surgery (median 56 days in the Netherlands).¹⁹ Patients who received nCRT other than the CROSS (ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study) protocol³ or who had received prior systemic therapy for the same tumor were excluded. Finally, patients with a clinical complete response after CRT with an intentional wait-and-see strategy were excluded (because distant metastases in this group were considered as recurrent disease rather than interval metastases).

STAGING. The Dutch national esophageal cancer guideline recommended routine baseline staging with ¹⁸F-FDG PET/CT since 2014.²⁰ Before 2014, guidelines recommended baseline staging with CT only. Although restaging after nCRT has not been part of the Dutch guideline, many institutions performed restaging as standard of care with either CT or ¹⁸F-FDG PET/CT.

VARIABLES. Data extracted from the NCR were patient characteristics including age, sex, year of diagnosis of the primary tumor, baseline World Health Organization performance score, and number of comorbidities. Disease characteristics including histology, location, clinical stage, and differentiation grade. Characteristics on interval metastases including the location and number of locations affected, the method of confirmation of distant metastases, as well as the time interval between start of nCRT and detection of distant metastases. The pattern of dissemination was categorized into hematogenous to a single organ or location only (eg, lung or bone),



peritoneum, extraregional lymph node, nonspecified single location, or multiple locations.

MANAGEMENT AND OUTCOMES. Management was categorized into metastasis-directed therapy (MDT), including systemic therapy, radiation therapy directed at metastasis, or metastasectomy; primary tumor resection; primary tumor resection plus MDT; or best supportive care (BSC). The OS was defined as the interval between moment of the detection of the primary tumor and death or last follow-up.

STATISTICAL ANALYSIS. Univariable and multivariable Cox proportional hazard models were used to identify prognostic factors (independently) associated with OS and were expressed using hazard ratio (HR) with 95% confidence interval (CI). For multivariable analysis, prognostic factors with a *P* value less than .25 in univariable analysis were entered in a model, and subsequent backward stepwise elimination based on the Akaike information criterion was performed.²¹ Kaplan-Meier curves were constructed of statistically significant prognostic factors in multivariable analysis.

For the secondary aim, patients with synchronous distant metastases from esophageal or gastroesophageal junction cancer were identified from the NCR (2010 to 2017) and nearest neighbor (1:3) propensity score-matching was performed to generate matched cases of the interval distant metastases cohort. A propensity score was generated using logistic regression, based on the covariates age, sex, year of diagnosis, location of primary tumor, histology, differentiation grade, clinical T-stage and N-stage, and number of locations with distant metastases. Propensity score matching was stratified for patients who received BSC and MDT. The within-pair difference was minimized by setting a caliper of 0.1 of the standard

deviation of the logit of the propensity score. Fisher's exact test and Kaplan-Meier curves with log rank tests were used to compare management and OS differences among the two groups. All statistical analyses were performed using R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), using the packages "survival" and "ggplot2." A *P* value of less than .05 was considered statically significant.

RESULTS

PATIENT INCLUSION. In all, 235 patients were eligible for inclusion (Figure 1). Subsequently, 19 patients were excluded because nCRT other than the CROSS regimen was used, 7 because distant metastases were detected during an intentional wait-and-see strategy, and 1 patient because of receiving prior systemic therapy for the same tumor. Consequently, 208 patients with interval distant metastases were included (7% of all patients who underwent nCRT).

PATIENT CHARACTERISTICS. Patients had a median age of 66 years (interquartile range [IQR], 59 to 71), 82% were male, and 82% had a baseline World Health Organization performance score of 0 to 1 (Table 1). The primary tumor was predominantly an adenocarcinoma (86%), located in the lower third of the thoracic esophagus (77%). The majority of patients were initially staged with cT3 (70%) and cN1 (39%) disease. Staging modalities included in addition to a baseline PET/CT, in 100% an endoscopy; in 59% endoscopic ultrasonography; and in 8% diagnostic laparoscopy. A total of 31 patients did not complete the entire CROSS protocol—patients prematurely stopped with chemotherapy (19), radiotherapy (4), or both (8).

CHARACTERISTICS OF INTERVAL DISTANT METASTASES.

The median time interval between detection of the primary tumor and detection of the first distant metastasis was 18 weeks (IQR, 16 to 21), and the interval between start of nCRT and detection of the first interval distant metastasis was 12 weeks (IQR, 10 to 14). In 98%, metastases were detected after nCRT. The method of confirmation of metastases was pathology (ie, histology or cytology) in 63% of cases. Dissemination was 38% hematogenous to one organ or location, 22% peritoneal, 12% extraregional lymph node, 5% to a single nonspecified location, and 24% to multiple locations (Table 2).

MANAGEMENT OF INTERVAL DISTANT METASTASES. In 87 patients (42%), MDT was initiated; 10%, primary tumor resection only; 7%, primary tumor resection plus MDT; and in 41%, BSC (Table 3). The MDT group consisted of patients who underwent systemic therapy (30%), radiation therapy (7%), chemoradiation therapy (4%), metastasectomy (1%), and

TABLE 1 Baseline Characteristics of Patients With Interval Distant Metastases

| Characteristic | Values (n = 208) |
|--|------------------|
| Age, years | 66 (59-71) |
| Sex | |
| Male | 171 (82.2) |
| Female | 37 (17.8) |
| Baseline performance score | |
| WHO 0 | 87 (41.8) |
| WHO 1 | 85 (40.9) |
| WHO 2 | 6 (2.9) |
| Missing | 30 (14.4) |
| Year of diagnosis primary tumor | |
| 2010-2014 | 48 (23.1) |
| 2015 | 43 (20.7) |
| 2016 | 58 (27.9) |
| 2017 | 59 (28.4) |
| Location of primary tumor | |
| Superior or mid third thoracic esophagus | 16 (7.7) |
| Lower third thoracic esophagus | 161 (77.4) |
| Gastroesophageal junction | 25 (12.0) |
| Thoracic esophagus not specified | 6 (2.9) |
| Clinical tumor stage | |
| cT1 | 1 (0.5) |
| cT2 | 49 (23.6) |
| cT3 | 146 (70.2) |
| cT4 | 7 (3.4) |
| Not specified | 5 (2.4) |
| Clinical nodal stage | |
| cN0 | 53 (25.5) |
| cN1 | 82 (39.4) |
| cN2 | 57 (27.4) |
| cN3 | 16 (7.7) |
| Histology | |
| Adenocarcinoma | 178 (85.6) |
| Squamous cell carcinoma | 30 (14.4) |
| Signet ring cell carcinoma | |
| No | 191 (91.8) |
| Yes | 17 (8.2) |
| Differentiation grade | |
| Well/moderate | 63 (30.3) |
| Poor | 80 (38.5) |
| Not specified | 65 (31.2) |

Values are median (interquartile range) or n (%). WHO, World Health Organization.

metastasectomy plus radiation therapy (1%). In 38% (80 of 208) metastases were detected during surgery. Of those, in 44% of patients (35 of 80), surgeons proceeded with resection of the primary tumor; and of those after surgery, in 43% of patients (15 of 35) MDT was applied (ie, primary tumor resection plus MDT); and in 57% of patients (20 of 35) after surgery, BSC was applied (ie, primary tumor resection only). The primary tumor resection plus MDT group consisted of patients who underwent primary tumor resection plus metastasectomy (2%), systemic therapy

TABLE 2 Characteristics of Interval Distant Metastases

| Characteristic | Values (n = 208) |
|---|------------------|
| Detection of interval distant metastases | |
| Weeks after diagnosis of primary tumor | 18 (16-21) |
| Weeks after start of nCRT | 12 (10-14) |
| During surgery | 80 (38.4) |
| Pattern of dissemination | |
| Single hematogenous location only | 79 (38) |
| Liver | 39 (18.8) |
| Bone | 17 (8.2) |
| Lung | 8 (3.9) |
| Soft tissue | 5 (2.4) |
| Brain | 3 (1.4) |
| Other hematogenous location | 7 (3.3) |
| Peritoneum only | 45 (21.6) |
| Extraregional lymph node only | 25 (12) |
| Head and neck only | 10 (4.8) |
| Intraabdominal only | 9 (4.3) |
| Other extraregional lymph node | 6 (2.9) |
| Single nonspecified location | 10 (4.8) |
| Multiple locations | 49 (23.6) |
| Method of confirmation | |
| Pathology | 132 (63.5) |
| Histology | 113 (54.3) |
| Cytology | 19 (9.1) |
| No pathology | 76 (36.5) |
| Intraoperatively detected without pathology | 3 (1.4) |
| Clinical diagnostic studies | 52 (25) |
| Not specified | 21 (10.1) |

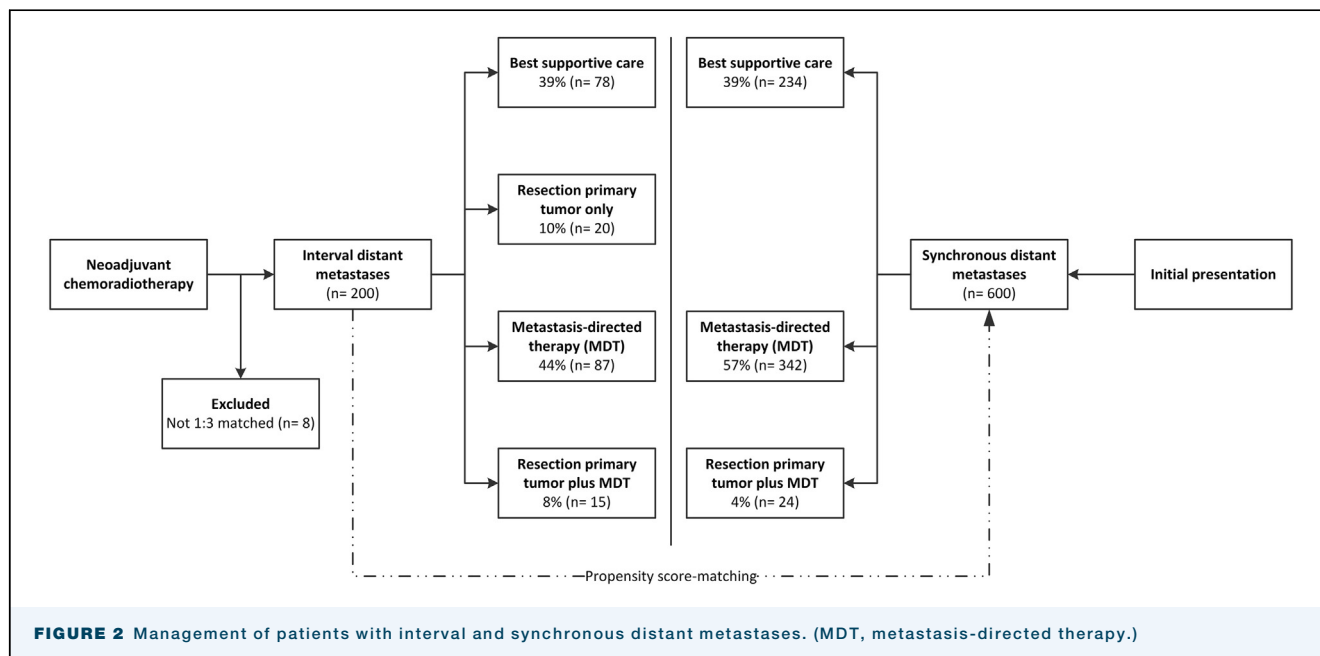
Values are median (interquartile range) or n (%). nCRT, neoadjuvant chemoradiotherapy.

(1%), metastasectomy and radiation therapy (1%), radiation therapy (1%), or chemoradiation therapy

TABLE 3 Management of Patients With Interval Distant Metastases

| Management Category | Values (n = 208) |
|--------------------------------------|------------------|
| Metastasis-directed therapy | 87 (41.8) |
| Systemic therapy | 62 (29.8) |
| RT | 15 (7.2) |
| CRT | 8 (3.8) |
| Metastasectomy | 2 (1.0) |
| Metastasectomy and RT | 1 (0.5) |
| Primary tumor resection only | 20 (9.6) |
| Primary tumor resection plus MDT | 15 (7.2) |
| Resection plus metastasectomy | 5 (2.4) |
| Resection plus systemic therapy | 3 (1.4) |
| Resection plus metastasectomy and RT | 3 (1.4) |
| Resection plus RT | 2 (1.0) |
| Resection plus CRT | 2 (1.0) |
| Best supportive care | 86 (41.3) |

Values are n (%). CRT, chemoradiation therapy; MDT, metastasis-directed therapy; RT, radiation therapy.



(1%). [Supplemental Table 1](#) demonstrates the baseline characteristics stratified on the type of management, showing significant differences between the groups with regard to age, performance status, cT-stage, and location of metastases.

OS AND PROGNOSTIC FACTORS FOR OS OF INTERVAL DISTANT METASTASES. The median follow-up time was 10.1 months (range, 1 to 50). Median follow-up time for survivors was 17.7 months (IQR, 15.8 to 22.6). Median OS after the diagnosis of the primary tumor in patients with interval distant metastasis was 10 months (IQR, 8.6 to 11.1). In comparison with BSC, superior OS was independently associated with either MDT (HR 0.36; 95% CI, 0.26 to 0.49), primary tumor resection (HR 0.55; 95% CI, 0.33 to 0.94), and primary tumor resection plus MDT (HR 0.20; 95% CI, 0.10 to 0.38; [Figure 3A](#)). Worse OS was independently associated with a signet ring cell carcinoma (HR 1.92; 95% CI, 1.12 to 3.28; $P < .001$; [Figure 3B](#)) and poor differentiation grade (HR 1.96; 95% CI, 1.35 to 2.83; $P = .002$; [Figure 3C](#), [Table 4](#)). Sensitivity analysis demonstrated no difference in OS among 176 patients who completed the entire nCRT treatment as compared with 31 patients who did not complete the entire nCRT treatment ($P = .400$). The OS after the moment of detection of interval distant metastases was 5.3 months (IQR, 2.4 to 10.5).

MANAGEMENT AND OS IN COMPARISON WITH PATIENTS WITH SYNCHRONOUS DISTANT METASTASES. Propensity score matching among 200 patients with interval distant

metastases resulted in a matched cohort of 600 patients with synchronous distant metastases ([Figure 2](#); [Supplemental Table 2](#)). Median OS after the diagnosis of the primary tumor in 200 patients with interval distant metastases was comparable with 600 patients with synchronous distant metastases (10.2 versus 9.4 months, $P = .760$; [Figure 4](#)).

COMMENT

This study shows that interval distant metastases develop in 7% of esophageal or gastroesophageal junction cancer patients who underwent nCRT according to the CROSS protocol. The OS after the diagnosis of the primary tumor was 10 months. Independent prognostic factors for worse OS were signet ring cell carcinoma, poor differentiation grade, and lack of management in which metastases were treated. Median OS after the diagnosis of the primary tumor in patients with interval distant metastases was comparable with matched patients with synchronous distant metastases ($P = .760$).

The median OS of 200 interval metastatic patients (10.2 months) was comparable to that of 600 matched synchronous metastatic patients (9.4 months) and with previously reported OS rates of synchronous metastatic patients in either real-world populations (6 to 8 months^{15,22}) or clinical trials populations (11 months).²³ This comparable OS suggest that in patients with interval distant metastases, microscopic progression (undetectable with baseline staging) may already have occurred at the time of diagnosis of the primary tumor. Because all patients with interval distant metastases underwent

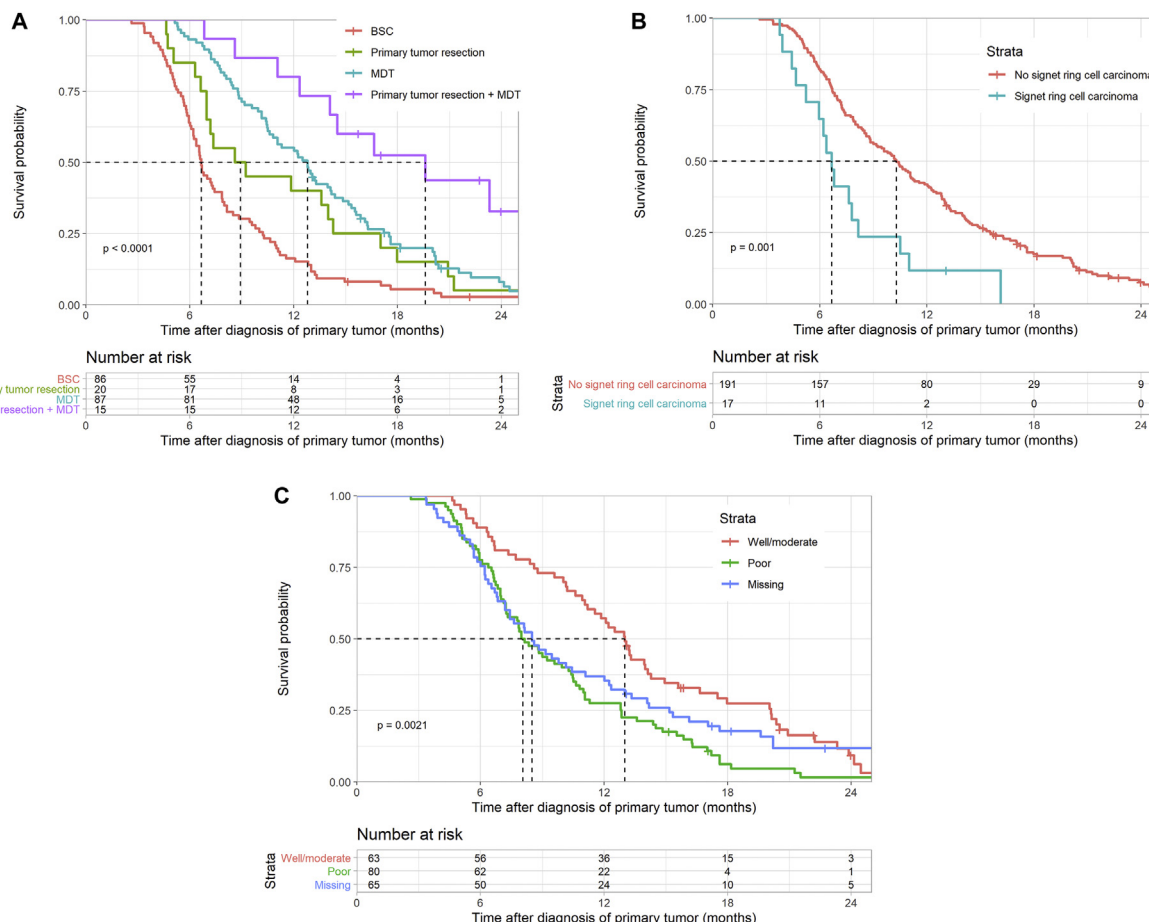


FIGURE 3 (A) Overall survival stratified by management: best supportive care (BSC [red line]); primary tumor resection (green line); metastasis-directed therapy (MDT [blue line]); or primary tumor resection plus MDT (purple line). (B) Overall survival stratified by signet ring cell carcinoma (blue line) or no signet ring cell carcinoma (red line). (C) Overall survival stratified on differentiation grade: well/moderate (red line); poor (green line); or missing (blue line).

baseline PET/CT imaging and in 8% diagnostic laparoscopy, we think this does not reflect inaccurate baseline staging but rather microscopic tumor progression (undetectable with baseline staging). In addition, the incidence of interval distant metastases after nCRT in this study (7%) was comparable with a meta-analysis of the detection of interval distant metastases in esophageal cancer patients who underwent neoadjuvant therapy and baseline and restaging PET/CT (8%).¹²

This study shows great heterogeneity in the type of management of patients with interval distant metastases. As many as 12 different types of management were initiated. Generally, OS was poor and physicians should reserve radical treatment for very carefully selected patients. In selected cases, primary tumor resection plus MDT was associated with an improved OS, possibly explained by an oligometastatic disease state.²⁴ Finally, restaging might be able to have an impact on treatment decision making and OS by earlier detection of distant

metastases and thereby earlier application of systemic treatment.¹³

Strengths of this study include the generalizability of the study cohort. In this study, patients were included who underwent nCRT according to the CROSS protocol only. Other strengths include data registration by specifically trained personnel and the prospectively maintained vital status owing to annual linkage with the municipal population registers. Finally, this study describes the largest population of esophageal or gastroesophageal junction cancer patients with interval distant metastases.

STUDY LIMITATIONS. There are certain limitations that apply to this study that warrant caution for the interpretation of results. Firstly, selection bias may have resulted in a potential overestimation of the effect of metastasis-directed therapy on OS. Secondly, because the NCR did not record the number of metastases per

TABLE 4 Results Cox Proportional Hazard Model Analysis for Overall Survival of Patients With Interval Distant Metastases

| Characteristic | Univariable | | Multivariable | |
|--|------------------|---------|------------------|---------|
| | HR (95% CI) | P Value | HR (95% CI) | P Value |
| Age ^a | 1.00 (0.98-1.02) | .734 | ... | |
| Sex | | | | |
| Male | Reference | | ... | |
| Female | 1.21 (0.82-1.75) | .332 | | |
| Baseline performance score | | | | |
| WHO 0 | Reference | | | |
| WHO 1-2 | 1.06 (0.78-1.44) | .669 | ... | |
| Missing | 1.20 (0.77-1.86) | .418 | ... | |
| Number of comorbidities ^a | 1.01 (0.89-1.13) | .880 | ... | |
| Clinical tumor stage | | | | |
| cT1-cT2 | Reference | | | |
| cT3-cT4 | 1.10 (0.78-1.54) | .583 | ... | |
| Missing | 1.54 (0.60-3.89) | .363 | ... | |
| Clinical nodal stage | | | | |
| cN0 | Reference | | Reference | |
| cN1 | 1.09 (0.76-1.57) | .632 | 1.06 (0.72-1.57) | .772 |
| cN2-cN3 | 1.37 (0.94-1.98) | .092 | 1.49 (0.99-2.22) | .053 |
| Year of diagnosis primary tumor ^a | 1.02 (0.94-1.10) | .589 | ... | |
| Location primary tumor | | | | |
| Superior or mid third esophagus | Reference | | | |
| Lower third esophagus | 0.69 (0.41-1.16) | .160 | ... | |
| Gastroesophageal junction | 0.53 (0.28-1.01) | .057 | ... | |
| Esophagus not specified | 0.59 (0.21-1.61) | .303 | ... | |
| Signet ring cell carcinoma | | | | |
| No | Reference | | Reference | |
| Yes | 2.37 (1.41-4.00) | <.001 | 1.92 (1.12-3.28) | .017 |
| Histology | | | | |
| Adenocarcinoma | Reference | | | |
| Squamous cell carcinoma | 1.15 (0.78-1.74) | .456 | ... | |
| Differentiation grade | | | | |
| Well/moderate | Reference | | Reference | |
| Poor | 1.84 (1.30-2.61) | .001 | 1.96 (1.35-2.83) | <.001 |
| Not specified | 1.35 (0.92-1.95) | .115 | 1.29 (0.88-1.91) | .194 |
| Type of dissemination | | | | |
| Single hematogenous location | Reference | | | |
| Peritoneum only | 1.10 (0.75-1.62) | .611 | ... | |
| Extraregional lymph node only | 1.02 (0.64-1.64) | .916 | ... | |
| Nonspecified single location | 0.92 (0.48-1.79) | .813 | ... | |
| Multiple locations | 1.03 (0.71-1.50) | .869 | ... | |
| Management | | | | |
| Best supportive care | Reference | | Reference | |
| Metastasis-directed therapy | 0.37 (0.27-0.50) | <.001 | 0.36 (0.26-0.49) | <.001 |
| Resection of primary tumor only | 0.51 (0.32-0.85) | .009 | 0.55 (0.33-0.94) | .027 |
| Resection primary tumor plus MDT | 0.22 (0.11-0.45) | <.001 | 0.20 (0.10-0.38) | <.001 |
| Method of confirmation | | | | |
| No pathology | Reference | | | |
| Pathology (ie, histology or cytology) | 0.80 (0.57-1.10) | .162 | ... | |
| Not specified | 1.04 (0.63-1.73) | .872 | ... | |

^aAnalyzed as continuous variable. CI, confidence interval; HR, hazard ratio; MDT, metastasis-directed therapy.

metastasis location, the impact of this potential prognostic factor on OS could not be assessed. Thirdly, because the NCR did not record the radiation dosage per fraction and the number of fractions, this study

was not able to discriminate between SBRT and palliative radiation therapy, which may have resulted in an underestimation of the effect of MDT on OS. Fourthly, because NCR did not record the performance

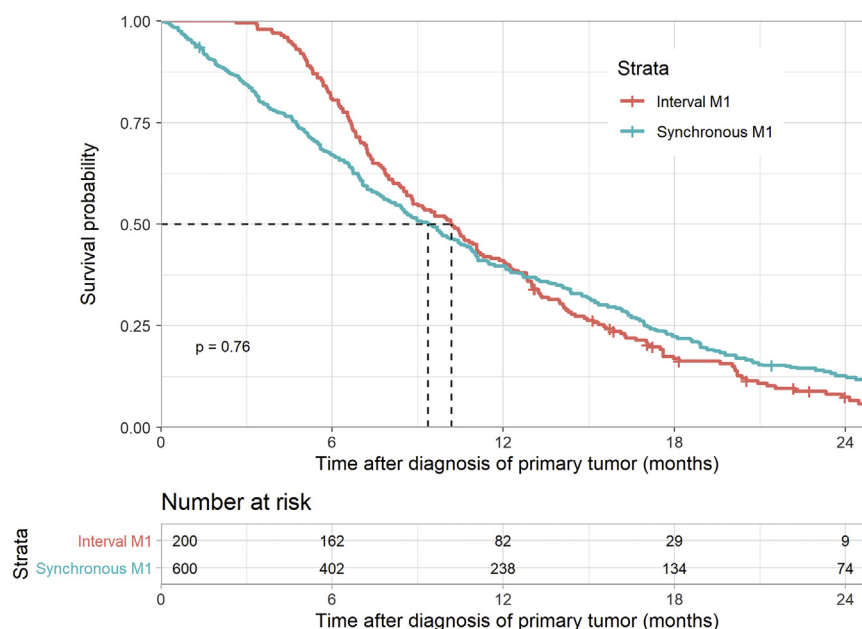


FIGURE 4 Overall survival after interval metastases (interval M1 [red line]) and synchronous distant metastases (synchronous M1 [blue line]).

status after nCRT, we were not able to use performance status as a matching variable in the propensity score matching. Finally, for some patients, the first modality of treatment may have been registered only because of registration practices. Therefore, this study may represent an underestimation of the complete (multimodality) treatment strategy.

CONCLUSION. Esophageal or gastroesophageal junction cancer patients with interval distant metastases after nCRT have a poor prognosis, with a median overall survival of 10 months after the diagnosis of the primary

tumor. In comparison with 600 matched patients with synchronous distant metastases, patients with interval distant metastases had comparable overall survival from the moment of diagnosis of the primary tumor.

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