Beyond Median Overall Survival: Estimating Trends for Multiple Survival Scenarios in Patients With Metastatic Esophagogastric Cancer

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ABSTRACT

Background: In recent years, clinical trials have shown improved survival of patients with metastatic esophageal or gastric cancer. The number of patients participating in clinical trials is limited, and survival improvements observed from clinical trials are unrepresentative for the full population. The aim of our study was to assess trends in survival for the best-case, typical, and worst-case scenarios in patients with metastatic esophageal or gastric cancer. **Methods:** We selected patients with metastatic esophageal or gastric cancer diagnosed between 2006 and 2020 from the nationwide Netherlands Cancer Registry. Survival was calculated for different percentiles of the survival curve for each incidence year (eg, the 10th percentile [p10] represents the top 10% of patients with the best survival): p10 (best-case), p25 (upper-typical), p50 (median), p75 (lower-typical), and p90 (worst-case). Weighted linear regression analyses were performed to test whether changes in survival were significant. **Results:** The overall median survival between 2006 and 2020 remained unchanged for patients with esophageal cancer (n=10,448; from 5.2 to 5.2 months, respectively; P=.06) and improved for patients with gastric cancer (n=10,512; from 3.5 to 4.3 months, respectively; P=.001). For patients with esophageal cancer, survival for the best-case scenario (p10; best 10% of patients) significantly improved from 17.2 to 21.0 months (P=.006). For patients with gastric cancer, survival significantly improved for the best-case scenario (p10) from 15.9 to 23.5 months (P<.001) and the upper-typical scenario (p25) scenario improved from 7.9 to 9.9 months (P<.001). **Conclusions:** Despite significant survival improvements in clinical trials, survival improvements were not observed for the majority of patients treated in daily clinical practice. An increase in survival was only observed for patients with the best prognosis.

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Background

For patients with metastatic esophageal or gastric cancer, palliative systemic therapy is superior to best supportive care (BSC) in terms of survival and can improve quality of life.[1–3] After the introduction of chemotherapy, novel palliative treatment strategies became available.[4–8] First-line therapy is administered in approximately 50% of patients with metastatic esophagogastric adenocarcinoma and approximately 30% of patients with metastatic esophageal squamous cell carcinoma.[9,10] After first-line treatment, 25% of patients proceed to second-line treatment.[11]

Fewer than 5% of patients participate in clinical trials, and because of strict inclusion criteria these patients are often younger and in better physical condition compared with those seen in daily practice.[12] Consequently, survival estimates from clinical trials are often unrepresentative of daily practice in contrast to population-based studies, which provide a complete representation of all patients.[13,14] A previous Dutch population-based study reported no change in median survival for patients with metastatic gastric cancer between 1990 and 2011.[15] For metastatic esophageal cancer, an improvement in median survival of 4 weeks was reported between 1989 and 2014.[16] These population-based studies are from a number of years ago, and novel treatments have become available since.[4,8] Furthermore, these studies focused on median overall survival (OS) or survival estimates after a certain number of years, in which a large range in survival is unrepresented. To explore survival beyond single-point estimates, the calculation of survival for multiple percentiles is valuable. Percentiles of the survival curve represent the period survived by a certain percentage of patients: for example, the 10th percentile (p10) represents the top 10% of patients with the best survival. Percentiles can be referred to as survival scenarios: best-case (p10), typical (p25–p75), and worst-case scenarios (p90).[17,18]


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To investigate whether advances in treatment have been beneficial and for which proportion of patients, we assessed trends over time regarding the best-case, typical, and worst-case survival scenario of patients with metastatic esophageal or gastric cancer in a population-based study. Furthermore, to place survival in perspective of the treatment landscape, trends in treatment are described.

Methods

Patients

Patients with synchronous metastatic esophageal (ICD-O-3 codes: C15.0–C15.9), gastroesophageal junction/cardia (C16.0), or gastric cancer (C16.1–C16.9) diagnosed between 2006 and 2020 were selected from the Netherlands Cancer Registry.[19] This registry serves the total Dutch population and is based on notification of all newly diagnosed malignancies by the national automated pathology archive. Additional information on diagnosis, stage, and treatment is extracted from medical records by data managers. Information on vital status was available through the linkage of the Netherlands Cancer Registry with the Dutch Personal Records Database and updated until February 1, 2022.

Patients diagnosed between 2006 and 2009, 2010 and 2016, and 2017 and 2020 were staged according to the sixth, seventh, and eighth editions of the IUCC *TNM Classification of Malignant Tumours*, respectively.[20–22] All patients with metastatic disease (cM1) were included, with the exception of those diagnosed as cM1a according to the sixth edition. The vast majority of these patients had a distal esophageal tumor with celiac lymph node metastases, which are regional lymph nodes (cN+) instead of extraregional lymph nodes (cM1) in the seventh and eighth versions.

Treatment

Treatment was mutually exclusive classified in the following order: palliative resection (resection of primary tumor ± perioperative treatment), chemoradiotherapy, systemic therapy, or BSC.

Statistical Analysis

Characteristics were noted with frequencies and percentages or mean and standard deviation. OS was assessed from the date of diagnosis until death or end of follow-up. OS was calculated for patients with esophageal and gastric (including gastroesophageal junction/cardia) cancer stratified by year of diagnosis and further stratified by treatment and histology (esophageal cancer only). A sensitivity analysis was performed for gastric cancer stratified by peritoneal metastases, because since 2016 a staging laparoscopy and FDG-PET/CT have been advised in patients with locally advanced tumors.[23] Staging laparoscopy improves the staging of M+, mostly for peritoneal metastases.[24]

Point estimates of OS for multiple percentiles of the survival curve were calculated for each year of diagnosis. The following percentiles were used to calculate survival scenarios: 10th (p10; best-case scenario), 25th (p25; upper-typical), 50th (p50; median), 75th (p75; lower-typical), and 90th (p90; worst-case scenario).[17,18,25]

Linear regression was performed to assess changes in treatment over time. Weighted linear regression was performed to obtain a trend line for survival of each scenario over time using the ggplot2 package for R using RStudio version 4.0.3 and R version 3.6.1 (R Foundation for Statistical Computing). The number of patients per year was used as weights. The slope of the trend line was tested for significance to investigate change over time. The cutoff point to perform weighted linear regression analysis was a minimum sample size of 2,250 patients between 2006 and 2020 (ie, an average of 150 patients per year). Two-sided *P* values of $<.05$ were considered statistically significant. All analyses were conducted using RStudio version 4.0.3 and R version 3.6.1 (R Foundation for Statistical Computing).

Results

Trends in Treatment

Between 2006 and 2020, 10,448 and 10,512 patients were diagnosed with metastatic esophageal or gastric cancer, respectively (Table 1). For esophageal cancer, the percentage of patients receiving BSC decreased from 68% in 2006 to 54% in 2020 ($P<.001$), whereas the percentage increased for systemic therapy (from 28% to 40%; $P<.001$) and chemoradiotherapy (from 2% to 5%; $P<.001$) (Figure 1A). The percentage of patients with esophageal cancer who underwent palliative resection remained stable (2% to 1%; $P=.10$). For gastric cancer, the percentage of patients receiving BSC remained stable (65% in 2006 to 55% in 2020; $P=.95$), whereas it increased for systemic therapy (from 28% to 42%; $P<.001$) and decreased for palliative resection (from 7% to 3%; $P<.001$) (Figure 1B).

For esophageal cancer, the use of systemic therapy increased among patients with adenocarcinoma (from 29% in 2006 to 48% in 2020; $P<.001$), although not among those with squamous cell carcinoma (from 25% to 20%; $P=.88$) (supplemental eFigure 1, available with this article at JNCCN.org). Among patients with esophageal squamous cell carcinoma, the use of chemoradiotherapy increased from 3% to 13% ($P<.001$).

Survival Trends in Esophageal Cancer

For patients with esophageal cancer (n=10,448), median OS remained unchanged (from 5.2 months in 2006 to 5.2 months in 2020; $P=.06$) (Table 2 and Figure 2). Survival significantly improved for the best-case scenario (p10), with an average increase of 0.32 months per year, from 17.2 months in 2006 to 21.0 months in 2020 ($P=.006$),

Table 1. Patient Characteristics

	Esophageal Cancer n (%)	Gastric Cancer[a] n (%)
Total, n	10,448	10,512
Sex		
Male	8,157 (78.1)	6,876 (65.4)
Female	2,291 (21.9)	3,636 (34.6)
Age, mean [SD]	67.5 [10.5]	68.5 [12.2]
Primary tumor location		
Esophageal	10,448 (100.0)	NA
GEJ or cardia	NA	3,274 (31.1)
Gastric	NA	7,238 (68.9)
Histology		
Adenocarcinoma	7,454 (71.3)	10,053 (95.6)
Squamous cell carcinoma	2,441 (23.4)	56 (0.5)
Carcinoma NOS	553 (5.3)	403 (3.8)
Number of metastatic sites		
1	5,841 (55.9)	6,759 (64.3)
2	2,854 (27.3)	2,485 (23.6)
≥3	1,637 (15.7)	1,133 (10.8)
Unknown	116 (1.1)	135 (1.3)
Location of metastases		
Nonregional lymph node	5,117 (49.0)	3,343 (31.8)
Liver	4,897 (46.9)	4,375 (41.6)
Lung	2,617 (25.0)	1,193 (11.3)
Bone	1,808 (17.3)	867 (8.2)
Peritoneal	625 (6.0)	4,397 (41.8)
Other locations	1,628 (15.6)	1,095 (10.4)

Abbreviations: GEJ, gastroesophageal junction; NA, not applicable; NOS, not otherwise specified.
[a]Including GEJ cancer.

whereas it decreased for the lower-typical (average decrease of 0.03 months per year from 2.2 to 1.9 months; $P<.001$) and worst-case scenarios (average decrease of 0.02 months per year from 1.0 to 0.7 months; $P=.001$). Survival for the other scenarios remained unchanged.

For patients with esophageal cancer receiving systemic therapy (n=3,445), survival for the worst-case scenario decreased an average of 0.05 months per year from 3.7 months in 2006 to 3.3 months in 2020 ($P=.004$) (Table 2). For patients with esophageal cancer receiving BSC (n=6,256), survival for all scenarios decreased.

For patients with esophageal adenocarcinoma (n=7,454), survival for the best-case scenario (p10) significantly improved, with an average increase of 0.43 months per year from 15.8 months in 2006 to 20.9 months in 2020 ($P=.001$) (supplemental eTable 1, Figure 3). For esophageal adenocarcinoma, survival for all scenarios remained unchanged for patients receiving systemic therapy (n=2,842) and decreased for patients receiving BSC (n=4,206), except the lower-typical scenario, which remained unchanged. For esophageal squamous cell carcinoma (n=2,441), survival of all scenarios remained unchanged (Figure 3, supplemental eTable 1). For esophageal squamous cell carcinoma, analyses stratified by treatment were not performed due to limited sample size.

Survival Trends in Gastric Cancer

For patients with gastric cancer (n=10,512), median OS improved from 2006 to 2020, with an average increase of 0.05 months per year from 3.5 to 4.3 months, respectively ($P=.001$) (Table 2, Figure 2). Survival for the best-case scenario improved, with an average increase of 0.42 months per year from 15.9 to 23.5 months ($P<.001$), and survival for the upper-typical scenario improved, with an average increase of 0.15 months per year from 7.9 to 9.9 months ($P<.001$). Survival for the lower-typical and worst-case scenarios remained unchanged.

For patients with gastric cancer receiving systemic therapy (n=3,930), survival for all scenarios improved, with the highest improvement for the best-case scenario (average increase of 0.60 months per year from 21.7 to 26.4 months; measured until 2019 because survival in 2020 could not be calculated due to limited follow-up). For patients with gastric cancer receiving BSC (n=6,055), survival for all scenarios decreased except the best-case scenario, which remained unchanged.

The number of patients with gastric cancer diagnosed with peritoneal metastases increased from 31% in 2006 to 49% in 2020 (supplemental eTable 2). Survival improved for the upper-typical and median scenarios among those with peritoneal metastases (n=4,397), and for the best-case scenario among those without peritoneal metastases (n=6,115) (supplemental eTable 3 and eFigure 2).

Discussion

In this population-based study, an increase in survival for the best-case scenario (p10) among patients with esophageal cancer and for the best-case scenario (p10), upper-typical scenario (p25), and median (p50) among patients with gastric cancer was observed between 2006 and 2020. Use of systemic therapy and chemoradiotherapy increased for esophageal cancer and use of systemic therapy increased for gastric cancer between 2006 and 2020. Clinicians may use outcomes of the best-case, typical, and worst-case scenarios as a prognostic basis to explain life expectancy to patients, which is more helpful than solely providing the median survival.

In esophageal adenocarcinoma, the proportion of patients receiving systemic therapy increased and survival for the best-case scenario improved, in contrast to

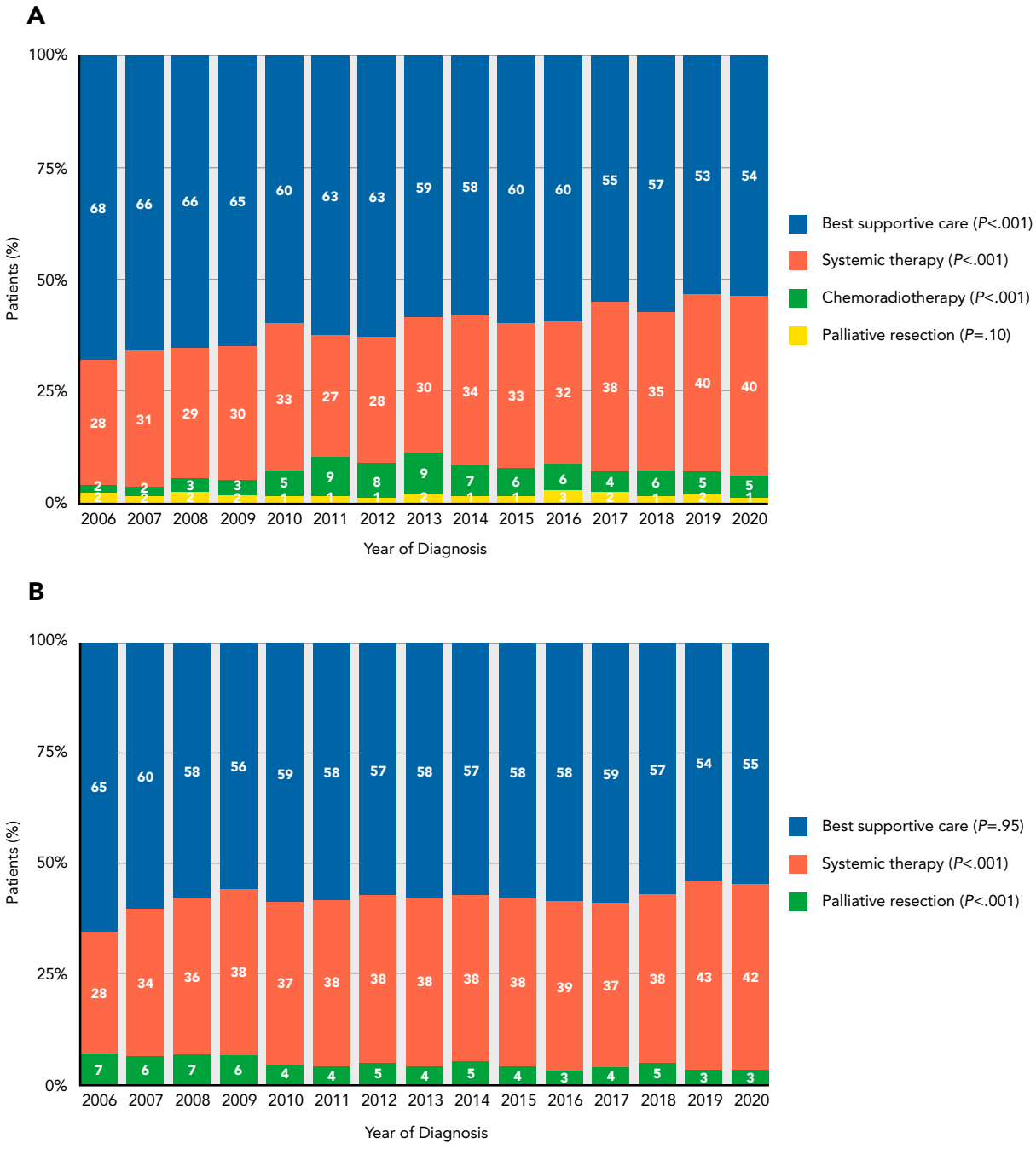

Figure 1. Treads of initial treatment in patients with metastatic **(A)** esophageal and **(B)** gastric cancers.[a]
P value represents the significance test for the linear trend analysis between 2006 and 2020.
[a]Patients with gastric cancer receiving chemoradiotherapy were excluded because this type of treatment was limited to ≤1% across all years.

esophageal squamous cell carcinoma, for which no increase in systemic therapy and no improvement in survival were observed. This finding could be due to the fact that evidence for palliative systemic therapy in esophageal squamous cell carcinoma has been scarce until recently.[5,26–29] Hopefully, the role of systemic therapy in esophageal squamous cell carcinoma will increase in the near future, given that clinical trials with PD-1 inhibitors have provided evidence for first-line and second-line treatment in subgroups of patients.[5,27,29]

Survival improvements for the scenarios for patients with esophageal cancer or esophageal adenocarcinoma receiving systemic therapy were not observed despite the increase in the use of systemic therapy. This finding is most likely due to a shift in the overall functional status of the population receiving systemic therapy, given that the percentage

Table 2. Patient Survival and Annual Average Change in Survival

	Overall Survival (mo)			Slope Estimate[a] (95% CI)	*P* Value
	2006	2020	2006–2020		
Esophageal cancer scenarios[b]					
All patients (n=10,448)					
Best-case (p10)	17.2	21.0	19.5	0.32 (0.12 to 0.52)	.006
Upper-typical (p25)	11.5	11.5	10.7	0.07 (−0.01 to 0.15)	.11
Median (p50)	5.2	5.2	5.1	−0.03 (−0.05 to −0.01)	.06
Lower-typical (p75)	2.2	1.9	2.1	−0.03 (−0.04 to −0.02)	<.001
Worst-case (p90)	1.0	0.7	0.9	−0.02 (−0.03 to −0.01)	.001
Systemic therapy (n=3,445)					
Best-case (p10)	19.5	24.1	25.4	0.14 (−0.32 to 0.60)	.57
Upper-typical (p25)	15.2	16.6	15.5	0.13 (−0.06 to 0.32)	.20
Median (p50)	10.9	10.0	9.4	0.02 (−0.08 to 0.12)	.74
Lower-typical (p75)	6.1	5.5	5.4	−0.05 (−0.11 to 0.01)	.09
Worst-case (p90)	3.7	3.3	3.1	−0.05 (−0.08 to −0.02)	.004
Best supportive care (n=6,256)					
Best-case (p10)	13.3	10.0	10.8	−0.19 (−0.3 to −0.08)	.005
Upper-typical (p25)	7.1	4.9	5.9	−0.13 (−0.16 to −0.1)	<.001
Median (p50)	3.5	2.3	2.9	−0.08 (−0.1 to −0.06)	<.001
Lower-typical (p75)	1.7	1.0	1.3	−0.04 (−0.05 to −0.03)	<.001
Worst-case (p90)	0.7	0.5	0.6	−0.02 (−0.03 to −0.01)	<.001
Gastric cancer scenarios[b]					
All patients (n=10,512)					
Best-case (p10)	15.9	23.5	17.2	0.42 (0.24 to 0.60)	<.001
Upper-typical (p25)	7.9	9.9	9.2	0.15 (0.10 to 0.20)	<.001
Median (p50)	3.5	4.3	3.9	0.05 (0.03 to 0.07)	.001
Lower-typical (p75)	1.4	1.4	1.5	−0.01 (−0.02 to 0.00)	.38
Worst-case (p90)	0.7	0.7	0.7	0.00 (−0.01 to 0.01)	.22
Systemic therapy (n=3,930)					
Best-case (p10)	21.7	26.4[c]	23.1	0.60 (0.28 to 0.92)	.003
Upper-typical (p25)	14.4	16.9	14.1	0.31 (0.17 to 0.45)	<.001
Median (p50)	8.1	9.0	8.3	0.13 (0.06 to 0.20)	.005
Lower-typical (p75)	4.6	5.6	4.8	0.07 (0.02 to 0.12)	.008
Worst-case (p90)	2.5	3.4	2.6	0.04 (0.01 to 0.07)	.02
Best supportive care (n=6,055)					
Best-case (p10)	8.3	6.3	8.2	−0.06 (−0.13 to 0.01)	.14
Upper-typical (p25)	4.5	3.5	4.2	−0.03 (−0.06 to 0.00)	.05
Median (p50)	2.2	1.6	1.9	−0.02 (−0.03 to −0.01)	.004
Lower-typical (p75)	1.1	0.8	0.9	−0.02 (−0.03 to −0.01)	<.001
Worst-case (p90)	0.6	0.4	0.4	−0.01 (−0.02 to 0.00)	.002

[a]The slope estimate represents the annual average survival change (months) between 2006 and 2020.
[b]Analyses for patients with esophageal or gastric cancer receiving palliative resection or chemoradiotherapy were not performed due to limited sample size.
[c]Survival in 2019, because the survival in 2020 could not be calculated due to limited follow-up; the slope estimate of this analysis is subsequently calculated from 2006 to 2019.

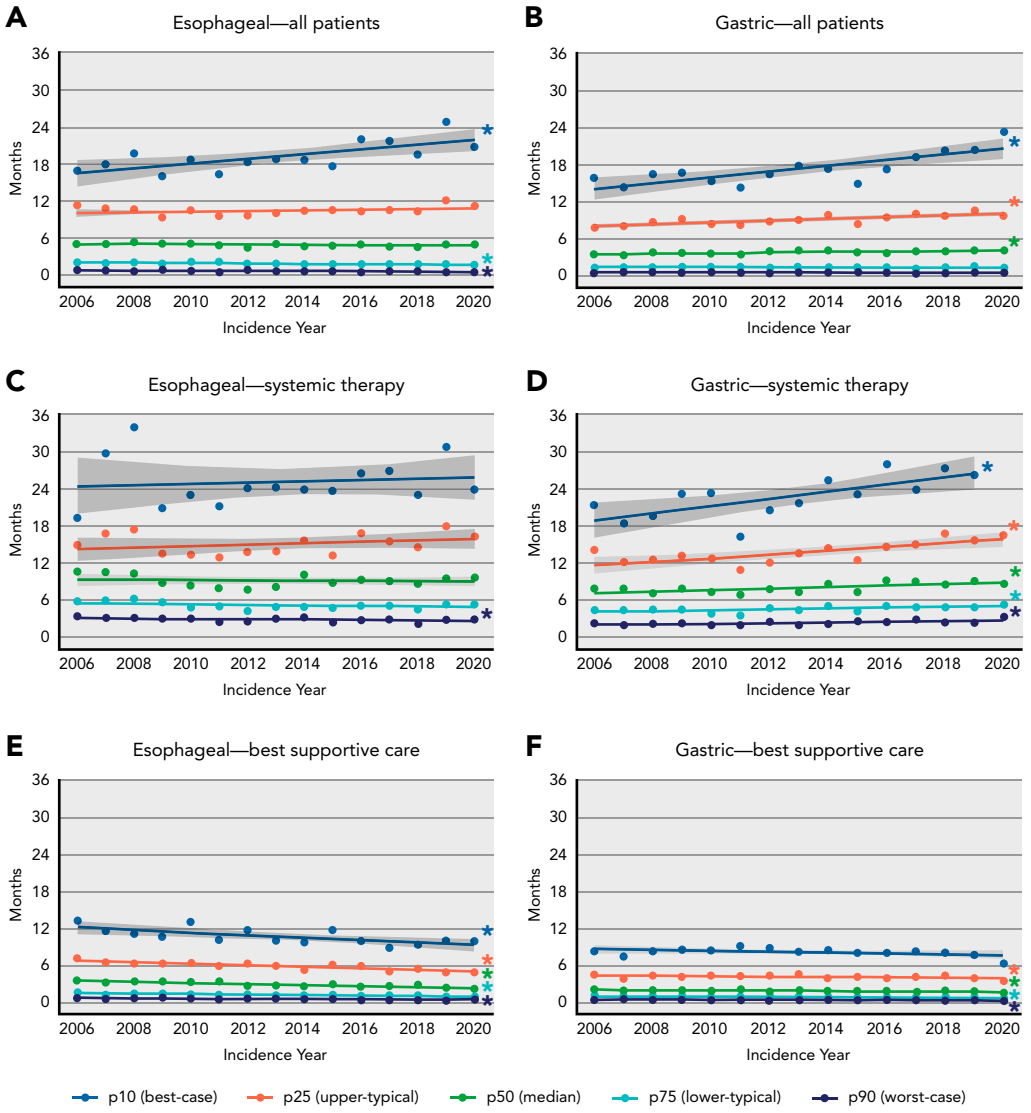

Figure 2. Survival of patients with **(A, C, E)** esophageal or **(B, D, F)** gastric cancer for different scenarios over time, stratified by percentile (p) of survival. For patients with gastric cancer receiving systemic therapy **(D)**, the highest percentile (p10, best-case scenario) for 2020 could not be displayed due to limited follow-up time.
*Significant trend of $P<.05$.

of patients receiving systemic therapy increased and the percentage of patients receiving BSC decreased. In other words, patients receiving systemic therapy in the later years probably had a poorer functional status and consequently worse outcomes compared with the patients receiving systemic therapy in the earlier years. Another possible explanation for the absence of survival improvement could be the lack of improvement in the efficacy of systemic therapy over time. Recently first-line nivolumab in combination with chemotherapy showed an improved survival of 3.3 months in patients with HER2-negative tumors and a PD-L1 combined positive score of ≥5, which could improve survival beyond the outcomes described in this study.[6]

In our study, the percentage of patients with gastric cancer receiving systemic therapy increased from 28% to 42% and median survival increased by 0.8 months between 2006 and 2020. An increase in the use of systemic therapy was previously reported from 5% in 1990 to 36% in 2011; however, the study did not report an increase in median survival.[15] Another Dutch population-based study reported an increase in median survival of 2.0 months for patients receiving systemic therapy between 1999 and 2017.[30] Observed survival improvements are probably the result of the availability of targeted agents, such as the improvements seen in the ToGA trial (2011) for trastuzumab and the RAINBOW trial (2016) for paclitaxel and ramucirumab.[4,8]

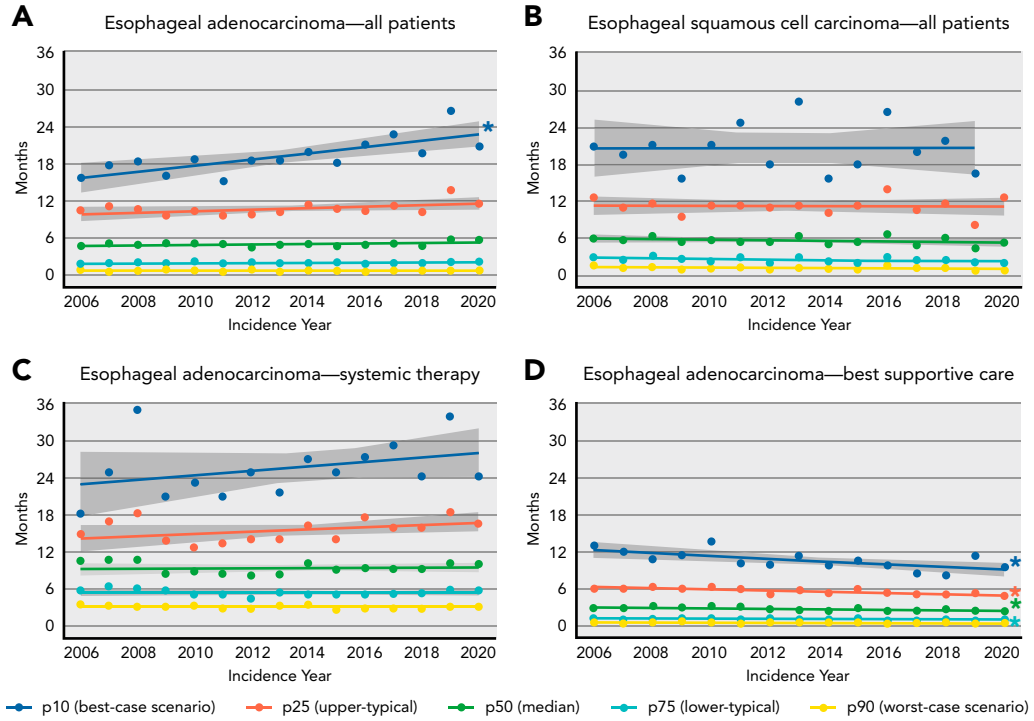

Figure 3. Survival of patients with **(A, C, D)** esophageal adenocarcinoma or **(B)** esophageal squamous cell carcinoma for different scenarios over time, stratified by percentile (p) of survival. For patients with esophageal squamous cell carcinoma **(B)**, the highest percentile (p10, best-case scenario) for 2020 could not be displayed because of limited follow-up time, and due to limited sample size, stratification according to type of treatment was not performed.
*Significant trend of $P<.05$.

Among patients with gastric cancer receiving systemic therapy, the survival benefits were largest in the best-case (p10; 4.7 months; until 2019) and upper-typical scenarios (p25; 2.5 months). The ToGA trial reported a survival improvement of 2.7 months and the RAINBOW trial reported an improved survival of 2.2 months.[4,8] These findings indicate that survival improvements observed in clinical trials only translate to a minority of patients in clinical practice (ie, approximately the top 25% of patients). Not all patients are eligible for treatment with trastuzumab; only approximately 15% to 25% have an HER2-positive tumor.[31] Similarly, approximately 25% of patients proceed to second-line treatment in clinical practice.[11] In addition, a small proportion of patients respond extremely well to trastuzumab, which can result in long-term survival of several years.[32,33] Survival outcomes are likely to improve in the near future; recent trials showed positive results for trastuzumab deruxtecan in previously treated HER2-positive gastric cancer and dual blockade of PD-1 and HER2 in first-line treatment.[34,35]

For patients with esophageal and gastric cancer receiving BSC, survival of those in the worst-case scenario (p90) was extremely poor at <1 month. This finding underscores the low probability of clinically meaningful treatment options in this population and the need for integrated advanced care planning.[36]

Our study shows a large variation in survival across the scenarios. Currently, it is unclear which factors determine how patients respond to systemic therapy, and it is unknown whether a patient will have a poor or good response (ie, which scenario will represent the survival). Therefore, clinicians should discuss survival according to multiple scenarios to better explain life expectancy to patients.[17,18,37] Previous research in patients with advanced cancer showed that patients prefer the presentation of survival according to multiple scenarios rather than the median survival.[37] Results from our study are useful for clinicians to inform patients of their life expectancy beyond the median OS. This information can be complementary to the use of clinical prediction models, such as SOURCE.[38] Perhaps in the future, prediction models or identification of biomarkers will better identify which patients should receive systemic treatment or will have a good response on therapy.

For both gastric and esophageal cancers, improvements in the diagnostic process have likely contributed to stage migration from nonmetastatic to metastatic disease due to earlier detection and detection of smaller metastases.[16,39] This is particularly true for peritoneal metastases, because a staging laparoscopy, which is essential for the

diagnosis of metastases in the peritoneum, was added to the Dutch guidelines for gastric cancer in 2016.[23,24,40] In our study, an increase in the presence of peritoneal metastases was observed for patients with gastric cancer between 2006 and 2020, in line with previous research.[30] However, before 2016, the percentage of patients diagnosed with peritoneal metastases had already increased (from 31% in 2006 to 44% in 2015; not tested for significance), indicating that before the implementation of staging laparoscopy, peritoneal metastases occurred more frequently. This development could be related to improved diagnostics and expertise by pathologists over time. In addition, it could be related to the shift in the type of gastric cancer, in that the proportion of patients diagnosed with a diffuse type increased and those diagnosed with an intestinal type decreased between 1989 and 2015 in the Netherlands, and the diffuse type more often metastasizes to the peritoneum compared with the intestinal type.[41,42]

The strength of our study is the use of population-based data as opposed to clinical trial data. Population-based data include information on frail and older adult patients and patients with comorbidities, whereas patients in clinical trials are often younger and have a better performance status.[13] In addition, outcomes of this study could probably be extrapolated to patients with (late) metachronous metastatic disease, because survival of these patients is similar to that of patients with synchronous metastatic disease.[9]

Our study has several limitations. First, reported point estimates of an individual year of diagnosis should be interpreted with caution because survival varied over the years, particularly for the best-case and worst-case scenarios because of the relatively small sample size. Second, the sample size of certain treatment groups was limited and therefore analysis was not performed. Third, information on performance status, comorbidities, and treatment details (type, dose, and duration) was unavailable. Finally, survival outcomes as presented in our study should not be used in treatment decisions due to the observational nature of our study.

Conclusions

In this study, survival improvements were not observed for most patients with metastatic esophageal or gastric cancer. However, at least an increase in survival was observed for patients with the best prognosis. By reporting survival according to multiple survival scenarios, we identified the proportion of patients who had the benefit of treatment advances over the past 15 years.

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References

1. Ter Veer E, Haj Mohammad N, van Valkenhoef G, et al. The efficacy and safety of first-line chemotherapy in advanced esophagogastric cancer: a network meta-analysis. J Natl Cancer Inst 2016;108:djw166.
2. van Kleef JJ, Ter Veer E, van den Boorn HG, et al. Quality of life during palliative systemic therapy for esophagogastric cancer: systematic review and meta-analysis. J Natl Cancer Inst 2020;112:12–29.
3. Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006;24:2903–2909.
4. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376:687–697.
5. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. N Engl J Med 2022; 386:449–462.
6. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:27–40.
7. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19:1437–1448.
8. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224–1235.
9. Pape M, Vissers PAJ, Bertwistle D, et al. A population-based study in synchronous versus metachronous metastatic esophagogastric adenocarcinoma. Ther Adv Med Oncol. Published online March 24, 2022. doi: 10.1177/17588359221085557
10. Pape M, Vissers PAJ, de Vos-Geelen J, et al. Treatment patterns and survival in advanced unresectable esophageal squamous cell cancer: a population-based study. Cancer Sci 2022;113:1038–1046.
11. Dijksterhuis WPM, Verhoeven RH, Pape M, et al. Hospital volume and beyond first-line palliative systemic treatment in metastatic oesophagogastric adenocarcinoma: a population-based study. Eur J Cancer 2020; 139:107–118.
12. Donnelly CB, Wotherspoon AC, Morris M, et al. A population-level investigation of cancer clinical trials participation in a UK region. Eur J Cancer Prev 2017;26:S229–235.
13. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - what is it and what can it tell us? N Engl J Med 2016;375:2293–2297.

14. Templeton AJ, Booth CM, Tannock IF. Informing patients about expected outcomes: the efficacy-effectiveness gap. J Clin Oncol 2020;38:1651–1654.
15. Bernards N, Creemers GJ, Nieuwenhuijzen GA, et al. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy. Ann Oncol 2013;24:3056–3060.
16. van Putten M, de Vos-Geelen J, Nieuwenhuijzen GAP, et al. Long-term survival improvement in oesophageal cancer in the Netherlands. Eur J Cancer 2018;94:138–147.
17. Hamers PAH, Elferink MAG, Stellato RK, et al. Informing metastatic colorectal cancer patients by quantifying multiple scenarios for survival time based on real-life data. Int J Cancer 2021;148:296–306.
18. Kiely BE, Soon YY, Tattersall MH, et al. How long have I got? Estimating typical, best-case, and worst-case scenarios for patients starting first-line chemotherapy for metastatic breast cancer: a systematic review of recent randomized trials. J Clin Oncol 2011;29:456–463.
19. Fritz A, Percy C, Jack A, et al. International Classification of Diseases for Oncology, 3rd ed. Geneva, Switzerland: World Health Organization; 2000.
20. Sobin LH, Gospodarowicz MK, Wittekind C, eds. TNM Classification of Malignant Tumours, 7th ed. Hoboken, NJ: Wiley-Blackwell; 2009.
21. Brierley JD, Gospodarowicz MK, Wittekind C, eds. TNM Classification of Malignant Tumours, 8th ed. Hoboken, NJ: Wiley-Blackwell; 2016.
22. Sobin LH, Wittekind C, eds. TNM Classification of Malignant Tumours, 6th ed. Hoboken, NJ: Wiley-Liss; 2002.
23. Federation of Medical Specialists. Guidelines database - gastric carcinoma. Accessed January 5, 2022. Available at: https://richtlijnendatabase.nl/richtlijn/maagcarcinoom/algemeen.html
24. Gertsen EC, Brenkman HJF, van Hillegersberg R, et al. 18F-fludeoxyglucose-positron emission tomography/computed tomography and laparoscopy for staging of locally advanced gastric cancer: a multicenter prospective Dutch cohort study (PLASTIC). JAMA Surg 2021;156:e215340.
25. Williams M, Singer RA, Lerner A. A simple technique to estimate best- and worst-case survival in patients with metastatic colorectal cancer treated with chemotherapy. Ann Oncol 2014;25:2014–2019.
26. Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. Lancet Oncol 2020;21:832–842.
27. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial [erratum in Lancet Oncol 2019;20:e613]. Lancet Oncol 2019;20:1506–1517.
28. Kojima T, Shah MA, Muro K, et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. J Clin Oncol 2020;38:4138–4148.
29. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study [erratum in Lancet 2021;398:1874]. Lancet 2021;398:759–771.
30. Koemans WJ, Lurvink RJ, Grootscholten C, et al. Synchronous peritoneal metastases of gastric cancer origin: incidence, treatment and survival of a nationwide Dutch cohort. Gastric Cancer 2021;24:800–809.
31. Dijksterhuis WPM, Verhoeven RH, Meijer SL, et al. Increased assessment of HER2 in metastatic gastroesophageal cancer patients: a nationwide population-based cohort study. Gastric Cancer 2020;23:579–590.
32. Haider S, Ahmad H, Shah S, et al. Robust anti-tumor response in a patient with metastatic gastroesophageal junction adenocarcinoma on long-term maintenance chemotherapy with trastuzumab alone: an unusual occurrence. Cureus 2020;12:e11472.
33. Müller V, Clemens M, Jassem J, et al. Long-term trastuzumab (Herceptin) treatment in a continuation study of patients with HER2-positive breast cancer or HER2-positive gastric cancer. BMC Cancer 2018;18:295.
34. Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature 2021;600:727–730.
35. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382:2419–2430.
36. Kroon LL, van Roij J, Korfage IJ, et al. Perceptions of involvement in advance care planning and emotional functioning in patients with advanced cancer. J Cancer Surviv 2021;15:380–385.
37. Kiely BE, McCaughan G, Christodoulou S, et al. Using scenarios to explain life expectancy in advanced cancer: attitudes of people with a cancer experience. Support Care Cancer 2013;21:369–376.
38. van den Boorn HG, Abu-Hanna A, Haj Mohammad N, et al. SOURCE: prediction models for overall survival in patients with metastatic and potentially curable esophageal and gastric cancer. J Natl Compr Canc Netw 2021;19:403–410.
39. Dassen AE, Dikken JL, Bosscha K, et al. Gastric cancer: decreasing incidence but stable survival in the Netherlands. Acta Oncol 2014;53:138–142.
40. Machairas N, Charalampoudis P, Molmenti EP, et al. The value of staging laparoscopy in gastric cancer. Ann Gastroenterol 2017;30:287–294.
41. Koemans WJ, Luijten JCHBM, van der Kaaij RT, et al. The metastatic pattern of intestinal and diffuse type gastric carcinoma—a Dutch national cohort study. Cancer Epidemiol 2020;69:101846.
42. van der Kaaij RT, Koemans WJ, van Putten M, et al. A population-based study on intestinal and diffuse type adenocarcinoma of the oesophagus and stomach in the Netherlands between 1989 and 2015. Eur J Cancer 2020;130:23–31.

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Supplemental online content for:

Beyond Median Overall Survival: Estimating Trends for Multiple Survival Scenarios in Patients With Metastatic Esophagogastric Cancer

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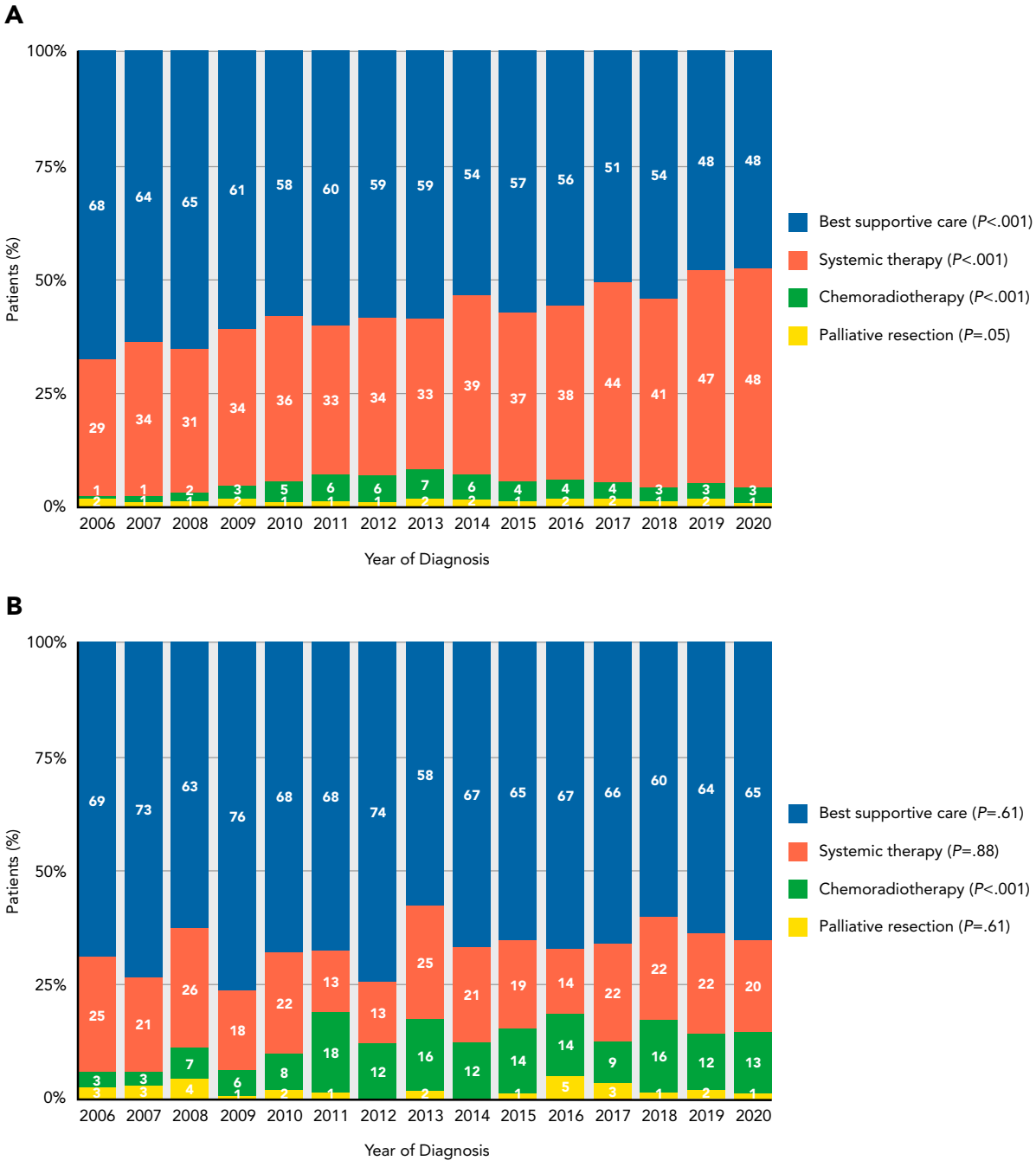
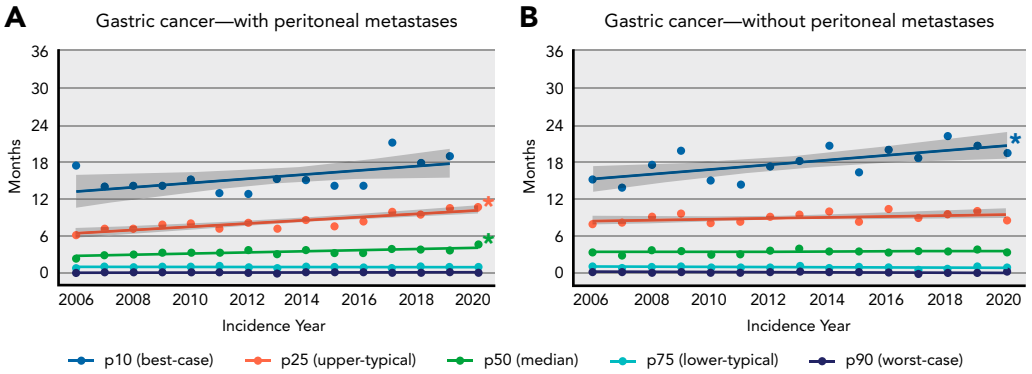


eFigure 1. Trends in initial treatment in patients with **(A)** esophageal adenocarcinoma and **(B)** esophageal squamous cell carcinoma. *P* value represents the significance test for the linear trend-analysis between 2006 and 2020.



eFigure 2. Overall survival of patients with gastric cancer **(A)** with and **(B)** without peritoneal metastases for different scenarios over time, stratified by percentile (p) of survival. For patients with peritoneal metastases **(A)** the highest percentile (p10, best-case scenario) for 2020 could not be displayed due to limited follow-up time.
*Significant trend of $P<.05$.

eTable 1. Survival of Patients With Esophageal Adenocarcinoma and Annual Average Change in Survival

	Overall Survival (mo)			Slope Estimate[a] (95% CI)	*P* Value
	2006	2020	2006–2020		
Esophageal adenocarcinoma scenarios[b]					
All patients (n=7,454)					
Best-case (p10)	15.8	20.9	19.5	0.43 (0.22 to 0.64)	.001
Upper-typical (p25)	10.6	11.7	10.9	0.08 (−0.02 to 0.18)	.14
Median (p50)	4.8	5.8	5.2	0.02 (−0.02 to 0.06)	.27
Lower-typical (p75)	1.9	2.4	2.2	0.01 (−0.01 to 0.03)	.19
Worst-case (p90)	0.9	1.0	0.9	0.00 (−0.01 to 0.01)	.81
Systemic therapy (n=2,842)					
Best-case (p10)	18.3	24.1	25.7	0.36 (−0.15 to 0.87)	.20
Upper-typical (p25)	14.9	16.7	15.9	0.20 (0.00 to 0.40)	.06
Median (p50)	10.5	10.1	9.5	0.05 (−0.05 to 0.15)	.28
Lower-typical (p75)	5.9	5.8	5.5	0.00 (−0.06 to 0.06)	.97
Worst-case (p90)	3.7	3.4	3.2	−0.03 (−0.07 to 0.01)	.16
Best supportive care (n=4,206)					
Best-case (p10)	13.2	9.6	10.6	−0.24 (−0.38 to −0.10)	.004
Upper-typical (p25)	6.1	4.9	5.7	−0.09 (−0.13 to −0.05)	<.001
Median (p50)	3.1	2.5	2.8	−0.05 (−0.08 to −0.02)	.008
Lower-typical (p75)	1.3	1.2	1.2	−0.01 (−0.02 to 0.00)	.07
Worst-case (p90)	0.7	0.6	0.6	−0.01 (−0.02 to 0.00)	.05
Esophageal squamous cell carcinoma scenarios[b]					
All patients (n=2,441)					
Best-case (p10)	20.7	16.4[c]	21.0	0.05 (−0.44 to 0.54)	.885
Upper-typical (p25)	12.6	12.6	11.0	−0.08 (−0.24 to 0.08)	.33
Median (p50)	5.9	5.2	5.5	−0.04 (−0.1 to 0.02)	.19
Lower-typical (p75)	2.9	2.0	2.4	−0.04 (−0.09 to 0.01)	.10
Worst-case (p90)	1.5	0.9	1.1	−0.02 (−0.05 to 0.01)	.32

[a]The slope estimate represents the annual average survival change (months) between 2006 and 2020.
[b]Analyses for patients with esophageal adenocarcinoma receiving palliative resection or chemoradiotherapy and esophageal squamous cell carcinoma receiving systemic therapy, best supportive care, palliative resection, or chemoradiotherapy were not performed due to limited sample size.
[c]Survival in 2019, because the survival in 2020 could not be calculated due to limited follow-up; the slope estimate of this analysis is subsequently calculated from 2006 to 2019.

eTable 2. Patients With Gastric Cancer Stratified by Presence of Peritoneal Metastases

Year of Diagnosis	With Peritoneal Metastases n (%)	Without Peritoneal Metastases n (%)
2006	192 (30.5)	438 (69.5)
2007	203 (32.3)	426 (67.7)
2008	252 (35.7)	453 (64.3)
2009	268 (37.6)	445 (62.4)
2010	280 (38.5)	448 (61.5)
2011	264 (37.0)	449 (63.0)
2012	291 (39.0)	455 (61.0)
2013	285 (41.8)	397 (58.2)
2014	301 (43.5)	391 (56.5)
2015	294 (43.7)	379 (56.3)
2016	321 (47.7)	352 (52.3)
2017	338 (48.5)	359 (51.5)
2018	358 (49.6)	364 (50.4)
2019	380 (50.8)	368 (49.2)
2020	370 (48.6)	391 (51.4)

eTable 3. Survival of Patients With Gastric Cancer Stratified by Presence of Peritoneal Metastases and Annual Average Change in Survival

	Overall Survival (mo)			Slope Estimate[a] (95% CI)	*P* Value
	2006	2020	2006–2020		
With peritoneal metastases survival scenarios (n=4,397)					
Best-case (p10)	17.7	19.2[b]	16.3	0.15 (−0.13 to 0.43)	.33
Upper-typical (p25)	6.6	11.1	8.9	0.25 (0.17 to 0.33)	<.001
Median (p50)	2.9	5.1	3.8	0.10 (0.06 to 0.14)	<.001
Lower-typical (p75)	1.3	1.5	1.5	0.00 (−0.01 to 0.01)	.99
Worst-case (p90)	0.6	0.6	0.6	0.00 (−0.01 to 0.01)	.67
Without peritoneal metastases survival scenarios (n=6,115)					
Best-case (p10)	15.5	19.7	17.9	0.39 (0.17 to 0.61)	.004
Upper-typical (p25)	8.3	9.0	9.4	0.08 (−0.01 to 0.17)	.08
Median (p50)	3.9	3.8	3.9	0.01 (−0.02 to 0.04)	.45
Lower-typical (p75)	1.5	1.4	1.4	−0.01 (−0.03 to 0.01)	.43
Worst-case (p90)	0.7	0.7	0.7	−0.01 (−0.02 to 0.00)	.26

[a]The slope estimate represents the annual average survival change (months) between 2006 and 2020.
[b]Survival in 2019, as the survival in 2020 could not be calculated due to limited follow-up; the slope estimate of this analysis is subsequently calculated from 2006 to 2019.