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Managed Clinical Network for esophageal cancer enables reduction of variation between hospitals trends in treatment strategies, lead time, and 2-year survival☆

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A B S T R A C T

Introduction: Despite evidence-based guidelines, variation in esophageal cancer care exists in daily practice. Many oncology networks deployed regional agreements to standardize the patient care pathway and reduce unwarranted clinical variation. The aim of this study was to explore the trends in variation of esophageal cancer care between participating hospitals of the Managed Clinical Network (MCN) in the Netherlands.
Materials and methods: Patients with esophageal cancer diagnosed from 2012 to 2016 were selected from the Netherlands Cancer Registry. Variation on treatment strategies, lead time to start of treatment, and 2-year survival, were calculated and compared between five clusters of hospitals within the network.
Results: A total of 1763 patients, diagnosed in 17 hospitals, were included. 71% of all patients received treatment with a curative intent, which ranged from 69% to 77% between the clusters of hospitals in 2015–2016. Although variation in treatment modalities between the clusters was observed in 2012–2014, no significant variation existed in 2015–2016, except for patients receiving no treatment at all. The 2-year overall survival of patients receiving treatment with a curative intent did not vary significantly between the clusters of hospitals (range: 56%–63%). Nevertheless, the median lead time before patients started treatment with a curative intent varied between clusters of hospitals in 2015–2016 (range: 34–47 days; $p < 0.001$).
Conclusion: Limited variation in esophageal cancer treatment between clusters of hospitals in the MCN existed. This study shows that oncology networks can promote standardization of cancer care and reduce variation between hospitals through insight into variation.

☆ The collaborating 17 hospitals in the MCN esophagogastric cancer in the North East region of the Netherlands are: Antonius Hospital, Sneek; Deventer Hospital, Deventer; Gelre Hospital, Apeldoorn/Zutphen; Isala Hospital, Zwolle; Martini Hospital, Groningen; Medical Center Leeuwarden, Leeuwarden; Medical Center Twente, Enschede; Hospital Ny Smellinghe, Drachten; Ommelander Hospital Group, Groningen/Delfzijl; Röpcke Zweers Hospital, Hardenberg; Queen Beatrix Hospital, Winterswijk; Hospital De Sionsberg, Dokkum; Treant Care Group, Hoogeveen; University Medical Center Groningen, Groningen; Wilhelmina Hospital Assen, Assen; Hospital Group Twente, Almelo/Hengelo; Hospital Tjongerschans, Heerenveen.

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1. Introduction

Esophageal cancer is the seventh most common cancer worldwide. Around 572,000 new cases of esophageal cancer were diagnosed globally in 2018, accounting for 3.2% of all new cases of cancer [1]. The incidence of esophageal cancer has risen in the Netherlands over the last years, approximately 2500 new cases of esophageal cancer were diagnosed in 2018 [2]. Survival rates are poor, mainly because esophageal cancer is usually diagnosed at a late stage [1,3].

Variation in care and treatment of patients with esophageal cancer exists. A previous study showed a large variation in the probability to undergo treatment with a curative intent for esophageal cancer which depended on the hospitals of diagnosis and which also affected the survival of these patients. In this study regional expert Multidisciplinary Team (MDT) meetings with involvement of experienced specialists were recommended for all patients with esophageal cancer [3].

The complexity of cancer care is increasing requiring expertise, skills and availability of technologies as well as (expensive) diagnostics and treatments. Moreover, hospitals are facing demands from external parties, such as volume norms and the increasing trend to publish results based on indicators and quality of care more transparently. Therefore, regional oncology networks were formed to maintain approachable access to care in all hospitals, to guarantee the quality of care regardless of the hospital of diagnosis, to refer patients to specialized center if needed, to improve accrual to clinical trials and to provide a platform for quality improvement [4].

Networks refer to a group of three or more organizations consciously formed, organized, and directed in ways to achieve a common goal [5]. Cancer services delivery is considered as a good example of network-based working because patients receive care from multiple health-care teams located in different settings [6,7]. Nevertheless, little evidence is available about the effects of networks in cancer care.

In the Netherlands many oncology networks have been established in recent years. In the North East region of the Netherlands a Managed Clinical Network (MCN) for patients with esophagogastric cancer was already founded in 2008. In this network 17 hospitals are collaborating, including teaching and non-teaching hospitals and one academic hospital. The aim of the MCN is to provide all esophagogastric cancer in the network easily accessible and equal care conform high quality standards and (inter)national guidelines. Therefore, the MCN regularly organizes meetings on a regional level to encourage knowledge exchange between the hospitals, initiates new agreements if necessary, carries out evaluations and stimulates MDT meetings. Within the MCN five regional MDT meetings occur, in which patients diagnosed with esophageal cancer from one or more hospitals, including a surgical treatment center, are jointly being discussed. All participating hospitals gave their commitment to formalized agreements leading to a standardized care pathway and treatment protocols, according to the Dutch Guidelines [8]. Five years after the establishment of the MCN differences between hospitals were observed, and the MCN members wondered whether these differences persisted in the following years.

In order to learn from the best practices and improve the care and treatment for patients with esophageal cancer care, the primary aim of this study was to gain insight in the variation of care between the clusters of hospitals within the MCN.

2. Materials and methods

In this study we used a retrospective research design. Patients with esophageal cancer receiving care from 2012 to 2014 within the MCN, were compared to 2015–2016. Patients were divided in five clusters of hospitals, based on the existing joint MDT meetings and the availability of a surgical treatment center within a cluster. In addition, outcomes of the MCN were compared with a national benchmark including all esophageal cancer patients in the Netherlands (including the MCN), to interpret the results of the regional network more accurate. The same patient selection criteria were applied for both the MCN and the national benchmark.

2.1. Data source

Data registered in the Netherlands Cancer Registry (NCR) were used to perform the analyses. This population-based registry covers the complete Dutch population (79 hospitals) and is based on a notification of all newly diagnosed malignancies in the Netherlands by the Dutch Nationwide Pathology Databank (PALGA). Additional notification sources are the national registry of hospital discharge and radiotherapy institutions. Specially trained data managers of the NCR routinely extract information on diagnosis, tumor stage, and treatment directly from the medical records.

2.2. Patient selection criteria

All patients with invasive potentially curable esophageal cancer (cT1-4a,cNany,cM0 & cTx,cNany,cM0, without cT1N0cM0) from 2012 to 2016 were selected from the NCR. The outcome lead time between diagnosis and start of the first treatment (chemoradiotherapy or resection) was restricted to patients with potentially curable esophageal cancer, who received treatment with a curative intent. All patients with early stage esophageal cancer (cT1 cN0 cM0) who usually underwent endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), were referred to endoscopic treatment and therefore differed from other surgical treatments (70 patients in 2012–2014; 50 patients in 2015–2016), were excluded from the dataset.

2.3. Outcome measures

Variation between 2012-2014 and 2015–2016 was analyzed for treatment modalities with and without a curative intent and lead time to start of treatment. Based on the Donabedian model the following indicators were arranged [9]:

Process indicator:

- Lead time from diagnosis (date diagnosis confirmed by pathology) to start of treatment with a curative intent.

Outcome indicators:

- For treatment with a curative intent strategies: patients receiving surgical treatment alone; patients receiving chemoradiotherapy without surgery; patients receiving surgery after neoadjuvant chemo(radio)therapy with or without adjuvant therapy.
- For treatment strategies without a curative intent: patients receiving treatments other than those mentioned above; patients receiving no treatment.
- 2-year overall survival.

2.4. Statistical analysis

For statistical testing between both periods the chi-squared test was used. Differences between characteristics were analyzed using chi-squared tests for nominal data and Mann-Whitney U tests for continuous data (based on median lead time and IQR). In case of small cell sizes (expected values less than 5), the Fisher's Exact test was used to calculate the association between categorical variables.

Statistical significant differences were calculated between: 1) the period 2012 to 2014 versus 2015 to 2016, 2) between the clusters of hospitals/surgical treatment centers within the MCN who discussed patients in a joint MDT meeting. In total five clusters of hospitals, ranging from one to five hospitals, were formed based on the existing regional MDT meetings. See Table 1.

The differences between treatment modalities over time and between the cluster of hospitals with the lowest and highest percentage of patients receiving treatment with or without a curative intent, were calculated by using the chi-squared test. These statistical differences were calculated for P1 and P2 separately. The log-rank test was used to test the variation of median lead time to start of treatment within the clusters over time and between the cluster of hospitals with the shortest and longest lead time to start of treatment with a curative intent.

In addition, Kaplan-Meier curves were generated to examine the overall survival over time. Survival curves were compared using the log-rank test. $P < 0.050$ was considered statistically significant. Besides, sensitivity analyses were performed to test whether the results of the MCN deviated from the national benchmark (including MCN). All analyses were conducted using STATA (StataCorp LLC, Texas, USA).

3. Results

A total of 1763 potentially curable esophageal cancer patients, diagnosed in the total period 2012 to 2016, were included. The median age of patients was 69 years. Apart from the shift in clinical stage over time ($p = 0.008$), no clinically relevant differences were observed for patients in the MCN (Table 2).

3.1. Differences in treatment modalities and lead time to start treatment

Out of 1763 patients, 68% of them received treatment with a curative intent in 2012–2014 and 71% in 2015–2016 (Table 3). In 2015–2016 less patients underwent surgical treatment alone (−4%; p:<0.001) and more patients received neoadjuvant chemo(radio) therapy and surgery with or without adjuvant therapy (+7%; $p = 0.005$) compared to 2012–2014. The latter group consisted of patients with two different treatment modalities, of which the largest group of patients received neoadjuvant chemoradiotherapy and surgery. Further, about 18% of all patients received chemoradiotherapy without surgery.

Treatment without a curative intent was given to 32% of all patients with potentially curable esophageal cancer in 2012–2014 and 29% in 2015–2016. Almost half of these patients received treatment for symptom relieve (i.e. non-curative radiotherapy or stent) and half of these patients did not receive any treatment at all.

The median lead time to the start of treatment with a curative intent reduced from 42 days in 2012–2014 to 41 days in 2015–2016 ($p = 0.040$) for patients with potentially curable esophageal cancer. See Table 3.

3.2. Sensitivity analyses

In comparison to the national population, the regional patient population appears to be a representative sample (see additional file 1). Additionally, in 2015–2016 more patients in the national population received treatment with a curative intent, compared to 2012–2014 (66% versus 70%, $p < 0.001$), which is comparable to the MCN region (68% and 71%). Nationwide trends in surgery only (−3%, $p < 0.001$), and neoadjuvant chemo(radio)therapy and surgery with or without adjuvant therapy (+5%, $p < 0.001$) were comparable to the MCN region. In comparison with the results of the MCN cohort which showed no differences over time for treatment with chemoradiotherapy without surgery, in the national benchmark significantly more patients received this treatment in 2015–2016 (+2%, $p = 0.008$).

The median lead time of patients to the start of treatment with curative intent reduced in the national cohort from 41 days in 2012–2014 to 40 days in 2015–2016 ($p < 0.001$) for patients with potentially curable esophageal cancer. This trend was comparable with the MCN region. See additional file 2.

3.3. Variation between clusters of hospitals

Significant variation, ranging from 63% to 78% between the clusters of hospitals, was observed for all patients receiving treatment with a curative intent in 2012–2014. In 2015–2016 these differences reduced with a range of 69% and 77% ($p = 0.11$). See Table 4. In addition, no variation existed between the clusters for patients receiving surgery only (0%–7%), chemoradiotherapy without surgery (15%–21%) and chemo(radio)therapy and surgery with or without adjuvant therapy (48%–53%) in 2015–2016. The proportion of patients receiving surgery only reduced significantly over time in cluster 2 (14% in 2012–2014 to 5% in 2015–2016, $p = 0.004$), cluster 3 (6% in 2012–2014 to 0% in 2015–2016, $p = 0.033$), and cluster 4 (8% in 2012–2014 to 3% in 2015–2016, $p = 0.049$). In cluster 2 significant more patients received neoadjuvant chemo(radio)therapy and surgery with or without adjuvant therapy in 2015–2016 (37% in 2014–2014 to 48% in 2015–2016, $p = 0.033$). See additional file 3.

Differences between the clusters for patients receiving other treatments varied from 14% to 16% in 2015–2016. In addition, for patients who did not receive any treatment at all, variation ranged from 9% to 17% in 2015–2016, which was a significant difference in both periods. The proportion of patients not receiving any

Table 1
Characteristics clusters of hospitals.

	Number hospitals included	Radiotherapy available within cluster	Linear accelerator available	PET-CT scan available
Cluster 1	5	✓	✓	✓
Cluster 2	4	✓	✓	✓
Cluster 3	1	no	no	✓
Cluster 4	4	✓	✓	✓
Cluster 5	3	✓	✓	✓

Table 2
Patient and tumor characteristics according to year of diagnosis for esophageal cancer.

Characteristics	Esophageal cancer MCN (n = 1763)		
	MCN 2012–2014 (n = 1022)	MCN 2015–2016 (n = 741)	*p*
Median age	69 (±10.81)	69 (±10.58)	*0.306*
Gender			
Male	749 (73%)	548 (74%)	*0.754*
Female	273 (27%)	193 (26%)	
Clinical TNM			
I	217 (21%)	143 (19%)	*0.008*
II	263 (26%)	196 (26%)	
III	402 (39%)	334 (45%)	
X	140 (14%)	68 (9%)	
Histology			
Adenocarcinoma	752 (74%)	542 (73%)	*0.705*
Squamous cell carcinoma	250 (24%)	188 (25%)	
Other	20 (2%)	11 (2%)	

Table 3
Treatment modalities and lead time to start treatment according to year of diagnosis for esophageal cancer.

	MCN 2012–2014 (n = 1022)	MCN 2015–2016 (n = 741)	*p*
Treatment with curative intent	697 (68%)	527 (71%)	0.189
Surgery only	72 (7%)	19 (3%)	*<0.001*
CRT[a] without surgery	177 (17%)	133 (18%)	*0.732*
Neoadjuvant C(R)T[a] & surgery with/without adjuvant therapy	448 (44%)	375 (51%)	*0.005*
Neoadjuvant C(R)T[a] & surgery	442	370	*0.005*
Neoadjuvant C(R)T[a] & surgery & adjuvant therapy	6	5	*0.817*
Treatment without curative intent	325 (32%)	214 (29%)	*0.189*
Other treatment	151 (15%)	108 (15%)	*0.907*
No treatment	174 (17%)	106 (14%)	*0.123*
Lead time to start of treatment with curative intent (median)	(n = 696) 42 (IQR:21.5)	(n = 527) 41 (IQR:17)	*0.040*

[a] CRT: Chemoradiotherapy; CT: Chemotherapy.

treatment reduced significantly in cluster 5 (16% in 2012–2014 to 9% in 2015–2016, p = 0.040). For more information, see additional file 3.

Furthermore, significant differences between the clusters of hospitals were found in the median lead time to start of treatment with a curative intent in both study periods (34 versus 54 days in 2012–2014, p < 0.001; 34 versus 47 days in 2015–2016; p < 0.001). Meanwhile, when focusing on the separate clusters, reduction in median lead time to the start of treatment with a curative intent was observed between 2014-2014 and 2015–2016 for hospital cluster 2 (54–47 days; p = 0.020), cluster 3 (40–34 days, p = 0.034), and cluster 4 (47–41 days; p = 0.010). For more details, see Table 4.

3.4. Variation in survival

The 2-year overall survival of patients receiving treatment with a curative intent ranged from 56% (cluster 2) to 63% (cluster 1 and 5) between the clusters of hospitals (additional file 4).

No significant differences between the 2-year overall survival were found between the hospital clusters. See Fig. 1.

The same applies for the 2-year overall survival of patients who received treatment without curative intent between the hospital clusters, these differences were not significant. See Fig. 2.

4. Discussion

Ten years after the foundation of the MCN esophagogastric cancer, we evaluated regional agreements regarding patients with esophageal cancer resulting in a standardized care pathway and treatment protocols, according to the Dutch Guidelines. The results of this study showed no differences in the proportion curative versus non-curative treatment over time. However, for patients who received treatment with a curative intent, less patients underwent surgical treatment only and more patients received neoadjuvant chemoradiotherapy and surgery over time. This observed trend in both the selected study years of 2012–2016 as well as in het national population, was conform the new standard of optimal treatment in the Netherlands based on the results of the CROSS trial [10] and therefore since 2010 formalized in the Dutch Guidelines. The shift from surgery only to neoadjuvant chemoradiotherapy and surgery, is confirmed in worldwide literature [11,12].

Although significant differences between all treatment modalities for potentially curable patients in the clusters of hospitals existed in the years 2012–2014, in the following years these differences reduced and no significant results were observed. The only exception to this was seen for patients who did not receive any treatment at all. In others studies more treatment variation was observed. For example, a recent study in Canada showed significant variation in treatment modality across hospitals, with esophagectomy ranging from 5% to 39%; esophagectomy after neoadjuvant therapy ranged from 33% to 93%; and esophagectomy followed by adjuvant therapy ranged from 0 to 34% [13], but also in Sweden pronounced differences in resection rates were noted between the Swedish geographical regions (ranging from 18.4% to 36.2% in 2016) [12]. In addition, neither significant differences between the 2-year survival occurred in the MCN region for patients receiving treatment with a curative intent nor for patients receiving treatment without a curative intent. In a previous study a large variation in the probability to undergo treatment with a curative

Table 4
Treatment modalities and lead time to start of treatment according to year of diagnosis for esophageal cancer.

	Curative treatment esophageal cancer MCN (n = 1763)			
	2012–2014 (P1[a]) (n = 1022)	2015–2016 (P2[a]) (n = 741)	*P1 versus P2* *p*	*Cluster lowest % versus cluster highest % p*
Total treatment with curative intent				
Cluster 1	(n = 222) 148 (67%)	(n = 196) 136 (69%)[low*]	*0.552*	
Cluster 2	(n = 197) 124 (63%)[low*]	(n = 155) 107 (69%)	*0.233*	
Cluster 3	(n = 98) 76 (78%)[high*]	(n = 72) 50 (69%)	*0.233*	*0.011 (P1)*
Cluster 4	(n = 251) 172 (69%)	(n = 145) 101 (70%)	*0.815*	*0.106 (P2)*
Cluster 5	(n = 254) 177 (70%)	(n = 173) 133 (77%)[high*]	*0.102*	
Total treatment without curative intent				
Cluster 1	74 (33%)	60 (31%)[high*]	*0.552*	
Cluster 2	73 (37%)[high*]	48 (31%)	*0.233*	
Cluster 3	22 (22%)[low*]	22 (31%)	*0.233*	*0.011 (P1)*
Cluster 4	79 (31%)	44 (30%)	*0.815*	*0.106 (P2)*
Cluster 5	77 (30%)	40 (23%)[low*]	*0.102*	
Lead time to start of treatment with curative intent	(n = 696)	(n = 527)		
Cluster 1	(n = 148) 42.5 (IQR:18)	(n = 136) 43.5 (IQR:18.5)	*0.612*	
Cluster 2	(n = 124) 54 (IQR:22)[high*]	(n = 107) 47 (IQR:18)[high*]	*0.020*	
Cluster 3	(n = 76) 40 (IQR:15.5)	(n = 50) 34 (IQR:12)	*0.034*	*<0.001 (P1)* *<0.001 (P2)*
Cluster 4	(n = 171) 47 (IQR:21)	(n = 101) 41 (IQR:14)	*0.010*	
Cluster 5	(n = 177) 34 (IQR:16)[low*]	(n = 133) 34 (IQR:14)[low*]	*0.984*	

[a] P1: 2012–2014; P2: 2015–2016; low: cluster of hospitals with the lowest percentage of patients receiving treatment with/without curative intent or the shortest median lead time to start of treatment with curative intent; high: cluster of hospitals with the highest percentage of patients receiving treatment with/without curative intent or the longest median lead time to start of treatment with curative intent.

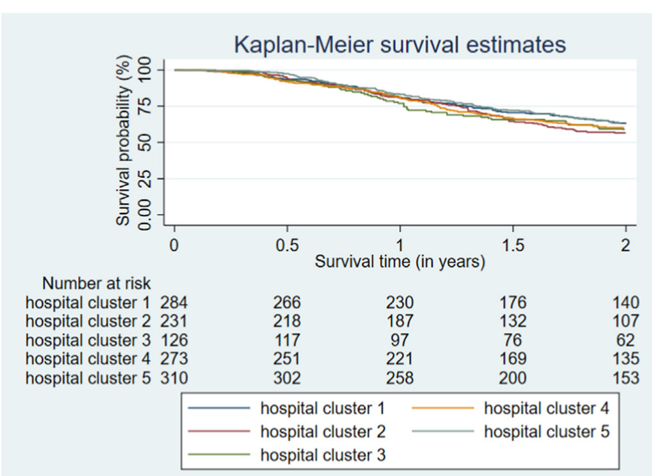

Fig. 1. Survival curve for patients receiving treatment with curative intent between clusters of hospitals.

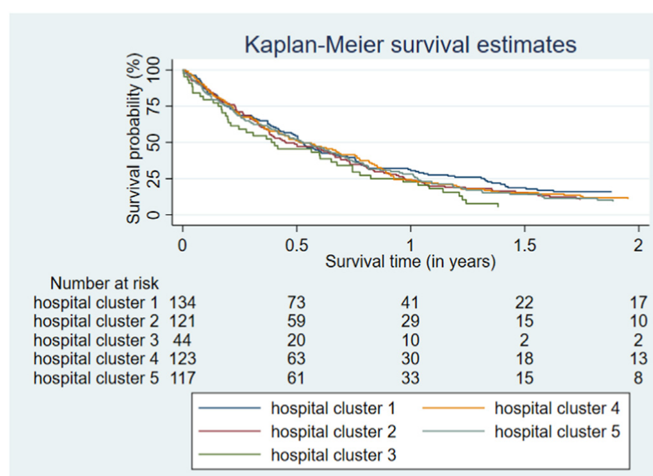

Fig. 2. Survival curve for patients receiving treatment without curative intent between clusters of hospitals.

intent for esophageal cancer between individual hospitals was revealed [3]. The present study showed that within the MCN potentially curable patients received treatment with a curative intent equally regardless of the hospital of diagnosis, suggesting that having clusters of hospitals around a regional MDT meeting has a positive effect on decreasing variation.

Within oncology networks the use of standardized pathways, quality improvement programs, and clinical trial resources are similarly increased [14]. Data provides enhanced analytic capabilities to facilitate greater understanding of care delivery outcomes [15]. In this study the MCN had a stimulating role in the regionalization of esophagogastric cancer care, and facilitated frequent insight in variation between (clusters of) hospitals which led to discussion about topics about the observed variation in previous years. In addition, literature confirms that sharing measurement of quality performance within an oncology network can be useful to assess the effectiveness of improvement initiatives [16]. Discussing data and variation has arose an awareness of standardization of care and discussing patients is a MDT meeting for exchange of expertise among the participants of the MCN. The formalization of regional agreements into a standardized care pathway was consisted with the goal of the network: to guarantee equal access and high quality of care in each hospital. Based on the results of this study, we assume that regionalization and standardization of care can lead to limited clinical variation and more equal care for esophageal cancer patients. Moreover, a continuous learning process serves as a platform for future collaboration and improvements.

Although the lead time to start of treatment reduced significantly in both MCN region and the national cohort with one day, variation was observed within the clusters of hospital showing that three hospital clusters achieved a significant reduction of median days to treatment. In other countries, longer lead times were observed, with less improvement over time. For example, data available in esophago-gastric cancer services in England and Wales in the UK, the median time from diagnosis to the start of primary curative therapy typically took between 1 and 2 months for surgical and oncological treatments. In addition, median waiting times from referral to treatment have not improved over the five year period from 2015/16 to 2019/20, for curative and non-curative treatments [17]. Meanwhile, the observed variation in lead time to start of treatment within a region can be a signal for improving the efficiency of care. Longer waiting times can be the result of suboptimal access to standard diagnostics, suboptimal coordination between the multidisciplinary team, or due to a more extensive diagnostic process sometimes based on trial protocols, or suboptimal access to treatment facilities. Moreover, in clinical practice variation exists in diagnostics trajectories not fastened in guidelines. For instance, some hospitals used endoscopic ultrasonography, as a routine in the workup, others perform these tool on demand. Similarly, current guidelines do not routinely advice geriatric assessment and cardiopulmonary exercise tests. Moreover, waiting times are frequently cited as a cause of patient dissatisfaction with the health care system [18] and reduction can be valuable from the patient's perspective. Besides, the relation waiting times before start treatment and patients' survival are controversial. Studies exists in which the influence of the delay of oncological therapy on cure and overall survival was confirmed [19,20]. In other studies, no evidence about this relation was available [21–23].

This study has several strengths and limitations. A strength of the study was the extensive dataset of the MCN which made it possible to perform statistical testing with larger patient groups. Moreover, a national benchmark was included, which helps to interpret the results on regional level more accurate. Based on this benchmark, the additionally performed sensitivity analysis showed no clinically relevant differences between the national benchmark and the MCN.

A limitation of this study was the selection of the limited number of two years which was used for follow-up. Using data covering more years would have given more insight in trends and variation over a longer period. Furthermore, the results of this study could be influenced by other factors, such published level 1 evidence, changes in protocols or the availability of related outcomes. In addition, the results presented in this study are not generalizable to other oncology networks, due to differences in patient population, regional agreements and organization of care processes.

5. Conclusion

This variation analysis provides insight in the reduction of variation between treatment modalities and patients' survival between clusters of hospitals within an oncology network over time. This study shows that reporting data and providing insight in variation within a region can lead to awareness of the health care professionals and contribute to achieve and the best optimal care for cancer patients, without unwarranted variation. Despite the fact that outcomes of a network as a whole may be similar to the national trend, this study shows that providing insight in variation of care between clusters of hospitals fits into a continuous learning process within an oncology network to identify areas of improvement in order to reach a higher level of cancer care and treatment for patients. Further opportunities to reduce variation between the clusters of hospitals were pointed out and provided a base for further collaboration and knowledge sharing about best practices between hospitals.

Additional files

1. Patient and tumor characteristics according to year of diagnosis for esophageal cancer; national benchmark
2. Treatment modalities and lead time to start treatment according to year of diagnosis for esophageal cancer; national benchmark
3. Treatment modalities with and without curative intent according to year of diagnosis for esophageal cancer; MCN
4 Overall survival for patients with potentially curable esophageal cancer; MCN

CRediT authorship contribution statement

Jolanda C. van Hoeve: Data curation, Formal analysis, Writing - review & editing. **Rob H.A. Verhoeven:** Data curation, Formal analysis, Writing – review & editing. **Wouter B. Nagengast:** Writing – review & editing. **Vera Oppedijk:** Writing – review & editing. **Mitchell G. Lynch:** Writing – review & editing. **Johan M. van Rooijen:** Writing – review & editing. **Patrick Veldhuis:** Writing – review & editing. **Sabine Siesling:** Data curation, Formal analysis, Writing – review & editing. **Ewout A. Kouwenhoven:** Data curation, Formal analysis, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.07.022.

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