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European Journal of Surgical Oncology 48 (2022) 435–448

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Nationwide oncological networks for resection of colorectal liver metastases in the Netherlands: Differences and postoperative outcomes

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ARTICLE INFO

Article history:
Received 9 April 2021
Received in revised form
29 August 2021

ABSTRACT

Introduction: Widespread differences in patient demographics and disease burden between hospitals for resection of colorectal liver metastases (CRLM) have been described. In the Netherlands, networks consisting of at least one tertiary referral centre and several regional hospitals have been established to

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[2] Shared senior author contributions.

https://doi.org/10.1016/j.ejso.2021.09.004
0748-7983/

Accepted 2 September 2021
Available online 9 September 2021

Keywords:
Oncological networks
Variation
Colorectal liver metastases
Outcomes

optimize treatment and outcomes. The aim of this study was to assess variation in case-mix, and outcomes between these networks.
Methods: This was a population-based study including all patients who underwent CRLM resection in the Netherlands between 2014 and 2019. Variation in case-mix and outcomes between seven networks covering the whole country was evaluated. Differences in case-mix, expected 30-day major morbidity (Clavien-Dindo ≥3a) and 30-day mortality between networks were assessed.
Results: In total 5383 patients were included. Thirty-day major morbidity was 5.7% and 30-day mortality was 1.5%. Significant differences between networks were observed for Charlson Comorbidity Index, ASA 3+, previous liver resection, liver disease, preoperative MRI, preoperative chemotherapy, ≥3 CRLM, diameter of largest CRLM ≥55 mm, major resection, combined resection and ablation, rectal primary tumour, bilobar and extrahepatic disease. Uncorrected 30-day major morbidity ranged between 3.3% and 13.1% for hospitals, 30-day mortality ranged between 0.0% and 4.5%. Uncorrected 30-day major morbidity ranged between 4.4% and 6.0% for networks, 30-day mortality ranged between 0.0% and 2.5%. No negative outliers were observed after case-mix correction.
Conclusion: Variation in case-mix and outcomes are considerably smaller on a network level as compared to a hospital level. Therefore, auditing is more meaningful at a network level and collaboration of hospitals within networks should be pursued.

1. Introduction

Resection of colorectal liver metastases (CRLM) is performed in 20–50% of all patients with CRLM and is the cornerstone of curative treatment [1,2]. Postoperative morbidity and mortality rates are still considerable in the Netherlands [3].

In the Netherlands, centralization of surgery was nationwide initiated and led by tumour specific committees on the basis of the standardisation report of the Dutch Federation of Oncologic Societies (SONCOS) [5]. During this process, liver surgery was centralized in 28 of 69 Dutch hospitals and seven oncological networks were formed for all oncological conditions [4,5]. The intention of these oncological networks was to optimize referral patterns between hospitals and to decrease hospital variation in preoperative and operative care [6]. As a result, quality of care for patients should be comparable in each oncological network.

Oncological networks for liver surgery consist of at least one tertiary referral centre performing liver surgery, several regional hospitals performing liver surgery and several regional hospitals not performing liver surgery [7]. Within oncological networks, tumour-specific multidisciplinary (MDT) meetings are attended by hepatobiliary physicians and surgeons according to the Dutch Guideline and the standardisation report of SONCOS with balanced patient-centered treatment plans developed by these teams [5,8]. Several oncological networks have specific agreements on preoperative workup, multidisciplinary team meetings, and criteria for referral of patients to more specialized care centres within the network. These oncological networks have synchronized guidelines and protocols between all hospitals in the oncological network. Other oncological networks have agreements on which hospitals perform which type of (tertiary) liver surgery, while preoperative workup and treatment can be hospital-specific [6,9].

The main objective of these oncological networks is to decrease variation in preoperative workup and treatment for CRLM which has been described in the Netherlands on a hospital level [7,10,11]. This variation is attributed to differences in patient demographics and disease burden (i.e. case-mix) of a hospital and translates to variation in treatment patterns and postoperative outcomes [12]. Due to oncological network formation, variation in case-mix on a hospital level has increased. Assessing quality of care on a hospital level could therefore pose problems. However, variation in case-mix might be comparable among oncological networks as each network serves the population of a region and has at least one tertiary care centre in the network to which complex cases are referred. Comparable workup and treatment in every oncological network might positively effect outcomes as patients receive standardised best-practice treatment independent of oncological network where treatment takes place. For these reasons, assessing quality of care on an oncological network level as well as auditing could be preferred.

The aim of this study was to assess variation in patient demographics and disease burden between oncological networks performing liver surgery and to compare differences in 30-day major morbidity and 30-day mortality between oncological networks.

2. Methods

This was a nationwide, population-based retrospective study performed in the Netherlands. The Netherlands is a country with approximately 17 million inhabitants. Health care is arranged in 69 hospitals including 8 university hospitals and 1 comprehensive cancer centre. Structural requirements for performing oncological care are established by SONCOS, endorsed by the Dutch Government and insurance companies [5]. These structural requirements for liver surgery include 24/7 availability of a skilled interventional radiologist, at least two skilled hepatobiliary surgeons, minimal procedural hospital volume requirements for liver resection (at least 20 liver resections per centre have to be performed annually for any indication) and participation in the Dutch Hepato Biliary Audit (DHBA); the mandatory audit in which all hospitals in the Netherlands performing liver surgery register all liver resections [13].

The 7 oncological networks in the Netherlands are based on topographical location and on agreements between hospitals (Fig. 1). All Dutch hospitals are included in an oncological network. Within oncological networks, agreements exist regarding hospitals with a tertiary referral status and the type of care that is delivered in the other hospitals. Variation exists between oncological networks regarding collaboration agreements. In several oncological networks, agreements concerning guidelines and referral criteria between hospitals have been established while in others every hospital performs care for hepatobiliary patients according to their own protocols. These collaboration agreements regarding preoperative workup and treatment of CRLM between oncological networks were assessed using a questionnaire.

Data for this study were collected from the DHBA. Data verification of the audit provided insight in completeness of 97% and

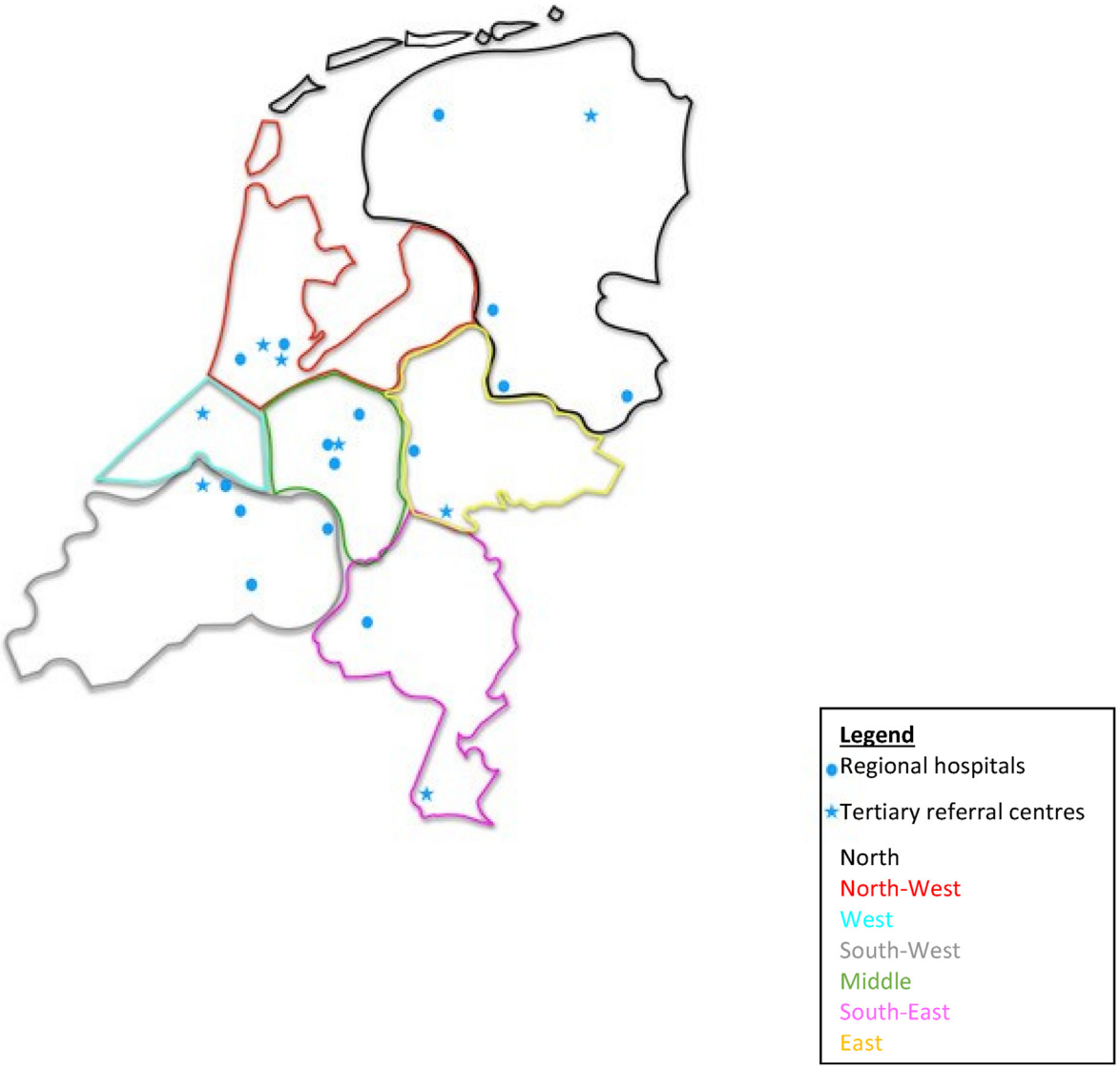

Fig. 1. Overview of the Dutch Oncological Networks. Only hospitals performing liver surgery are shown. Hospitals not performing liver surgery refer patients to regional hospitals. Tertiary referral centres perform more specialized and difficult types of care and often treat patients referred from regional hospitals.

accuracy of 96% in the DHBA when compared to the Dutch Cancer Registry [14]. No ethical approval was needed under Dutch law for this study.

2.1. Patient selection

All patients who underwent liver resection for CRLM between the 1st of January 2014 and 31st of December 2019 in the Netherlands and who were registered in the DHBA before 22nd of March 2020 were included in the study. Patients were excluded if information on date of surgery, type of tumour, or data regarding 30-day morbidity or 30-day mortality was missing. All patients who underwent thermal ablation without resection for CRLM were excluded.

2.2. Main outcomes

Main outcomes were variation in patient demographics, disease burden, 30-day major morbidity and 30-day mortality after liver resection. Major morbidity was defined as a complication Grade 3a or higher according to Clavien-Dindo classification, within 30 days after liver resection [15]. Mortality was defined as death during hospitalization or within 30 days after liver resection.

2.3. Variables

The case-mix of an oncological network can be explained by several factors: patient demographics, disease burden and treatment characteristics. Patient demographics included sex, age, American Society of Anesthesiologist (ASA) classification, Body Mass Index (BMI), comorbidity scores classified in the Charlson Comorbidity Index (CCI), histopathological classification of liver parenchyma adjacent to tumour tissue and previous liver surgery. Disease burden included number of CRLM, diameter of the largest CRLM before the initiation of tumour-specific treatment and synchronous (within 6 months of detection of the primary tumour) or metachronous diagnosis of the CRLM. Differences in treatment characteristics were assessed. These variables included use of preoperative MRI, use of preoperative chemotherapy, minor or major liver resection, combined liver resection and thermal

Table 1
Baseline characteristics of patients diagnosed with colorectal liver metastases (CRLM) between 2014 and 2019 in the Netherlands stratified for oncological network.

Factor		Network A	Network B	Network C	Network D	Network E	Network F	Network G	p-value
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Total		**1098**	**1189**	**1135**	**732**	**585**	**226**	**418**	
Patient characteristics									
Sex									0.390
	Male	710 (65)	738 (62)	727 (65)	477 (65)	354 (61)	144 (64)	255 (61)	
	Female	387 (35)	449 (38)	401 (35)	252 (35)	231 (39)	82 (36)	161 (39)	
	Missing[a]	1	2	7	3	0	0	2	
Age in years									0.050
	<50	63 (6)	99 (8)	89 (8)	53 (7)	41 (7)	11 (5)	30 (7)	
	50–64	374 (34)	426 (36)	380 (33)	261 (36)	192 (33)	79 (35)	159 (38)	
	65–79	592 (54)	567 (48)	573 (51)	365 (50)	306 (52)	128 (57)	191 (46)	
	≥80	66 (6)	95 (8)	92 (8)	53 (7)	45 (8)	8 (4)	36 (9)	
	Missing[a]	3	2	1	0	1	0	2	
Charlson Comorbidity Index (CCI)									**<0.001**
	0/1	836 (76)	926 (78)	871 (77)	546 (75)	428 (73)	170 (75)	239 (57)	
	≥2	262 (24)	263 (22)	264 (23)	186 (25)	157 (27)	56 (25)	179 (43)	
Body Mass Index (BMI)	Mean (sd)	26.7 (4.5)	25.9 (4.4)	26.3 (4.5)	26.3 (4.5)	26.1 (4.2)	26.4 (4.4)	26.4 (4.1)	**<0.001**
American Society of Anesthesiology (ASA) classification									**<0.001**
	ASA I/II	882 (80)	924 (81)	790 (74)	565 (77)	459 (78)	186 (86)	346 (84)	
	ASA III+	216 (20)	216 (19)	284 (26)	167 (23)	126 (22)	30 (14)	68 (16)	
	Missing[a]	0	49	61	0	0	10	4	
History of liver resection									**<0.001**
	No	873 (80)	956 (84)	913 (82)	544 (75)	467 (81)	192 (87)	354 (86)	
	Yes	213 (20)	182 (16)	205 (18)	180 (25)	108 (19)	30 (14)	57 (14)	
	Missing[a]	12	51	17	8	10	4	7	
Histopathology liver parenchyma[b]									**<0.001**
	Normal liver	727 (66)	872 (73)	747 (66)	329 (45)	354 (61)	120 (53)	318 (76)	
	Steatosis	170 (16)	162 (14)	189 (17)	160 (22)	69 (12)	38 (17)	68 (16)	
	Steato-hepatitis	20 (2)	19 (2)	4 (0)	28 (4)	6 (1)	7 (3)	2 (1)	
	Cirrhosis	5 (1)	10 (1)	5 (0)	6 (1)	2 (1)	2 (1)	10 (2)	
	Sinusoidal dilatation	8 (1)	30 (3)	7 (1)	8 (1)	4 (1)	0 (0)	0 (0)	
	Missing[a]	168	96	183	201	149	59	20	
Preoperative MRI									**<0.001**
	No	324 (30)	343 (31)	498 (44)	155 (26)	211 (37)	41 (20)	198 (49)	
	Yes	759 (70)	757 (69)	623 (56)	437 (74)	361 (63)	168 (80)	208 (51)	
	Missing[a]	15	89	14	140	13	17	12	
Preoperative chemotherapy									**<0.001**
	No	740 (71)	765 (71)	712 (66)	388 (57)	423 (77)	154 (77)	298 (75)	
	Yes	308 (29)	316 (29)	373 (34)	290 (43)	124 (23)	124 (23)	101 (25)	
Tumour characteristics									
Number of lesions									**<0.001**
	1	496 (46)	462 (41)	471 (42)	285 (42)	305 (53)	115 (53)	168 (44)	
	2	242 (22)	266 (24)	238 (22)	126 (19)	126 (19)	47 (22)	87 (23)	
	3	107 (10)	123 (11)	137 (12)	73 (11)	73 (11)	24 (11)	50 (13)	
	4	70 (7)	90 (8)	72 (7)	62 (9)	62 (9)	12 (6)	21 (6)	
	≥5	167 (15)	179 (16)	189 (17)	135 (20)	135 (20)	19 (9)	54 (14)	
	Missing[a]	16	69	28	51	7	9	38	
Maximum diameter of largest CRLM (mm[a])									0.050
	<20	339 (33)	313 (30)	310 (31)	138 (26)	172 (36)	74 (36)	99 (30)	
	20–34	408 (39)	372 (36)	357 (36)	209 (39)	175 (36)	71 (35)	135 (40)	
	35–54	191 (18)	215 (21)	199 (20)	118 (22)	83 (17)	36 (18)	57 (17)	
	≥55	100 (10)	131 (13)	123 (12)	75 (14)	52 (11)	24 (12)	44 (13)	
	Missing[a]	60	158	146	192	103	21	83	
Combined resection and ablation									**<0.001**
	No	909 (83)	887 (75)	811 (72)	647 (88)	516 (88)	185 (82)	318 (76)	
	Yes	189 (17)	302 (25)	324 (29)	85 (12)	69 (12)	41 (18)	100 (24)	
Major liver resection									**<0.001**
	No	831 (76)	951 (80)	926 (82)	593 (81)	418 (72)	191 (85)	294 (70)	
	Yes	267 (24)	238 (20)	209 (18)	139 (19)	157 (29)	35 (15)	124 (30)	
Location primary tumour									**<0.001**
	Colon	700 (64)	779 (66)	724 (64)	434 (59)	415 (71)	145 (66)	273 (65)	
	Rectal	397 (36)	308 (34)	407 (36)	298 (41)	169 (29)	74 (34)	145 (35)	
	Missing[a]	1	2	4	0	1	7	0	
Bilobair disease									**<0.001**
	No	651 (59)	610 (51)	636 (57)	315 (52)	358 (62)	143 (64)	250 (60)	
	Yes	447 (41)	578 (49)	473 (43)	295 (48)	219 (38)	81 (36)	166 (40)	
	Missing[a]	0	1	26	122	8	2	2	
Timing of metastases									0.090
	Metachronous	423 (47)	466 (49)	491 (52)	240 (50)	237 (49)	111 (59)	177 (39)	
	Synchronous	480 (53)	487 (51)	461 (48)	244 (50)	244 (51)	78 (41)	188 (52)	

Table 1 (*continued*)

Factor		Network A	Network B	Network C	Network D	Network E	Network F	Network G	p-value
		N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	
Total		**1098**	**1189**	**1135**	**732**	**585**	**226**	**418**	
	Missing[a]	195	236	183	248	104	37	53	
Extrahepatic disease									**<0.001**
	No	964 (89)	951 (84)	996 (89)	530 (87)	440 (83)	197 (92)	345 (87)	
	Yes	115 (11)	177 (16)	122 (11)	82 (13)	92 (17)	18 (18)	52 (13)	
	Missing[a]	19	61	17	120	53	11	21	
Surgical approach									**<0.001**
	Open	830 (76)	917 (78)	765 (68)	542 (75)	384 (66)	179 (80)	309 (75)	
	Laparoscopy	268 (24)	263 (22)	365 (32)	183 (25)	201 (34)	45 (20)	106 (25)	
	Missing[a]	0	9	5	7	0	2	3	
Type of hospital[c]									**<0.001**
	Regional hospitals	836 (76)	353 (30)	759 (67)	313 (43)	449 (77)	58 (26)	184 (44)	
	Tertiary referral centres	262 (24)	836 (70)	376 (33)	419 (57)	136 (23)	168 (74)	234 (56)	
Year of surgery									**<0.001**
	2014	147 (13)	188 (16)	218 (19)	120 (16)	78 (13)	29 (13)	79 (19)	
	2015	216 (20)	201 (17)	130 (12)	115 (16)	100 (17)	46 (20)	86 (21)	
	2016	213 (19)	244 (21)	194 (17)	159 (22)	100 (17)	43 (19)	23 (6)	
	2017	172 (16)	207 (17)	218 (19)	114 (16)	108 (19)	56 (25)	103 (25)	
	2018	176 (16)	206 (17)	187 (17)	127 (17)	100 (17)	33 (15)	72 (17)	
	2019	174 (16)	143 (12)	188 (17)	97 (13)	99 (17)	19 (8)	55 (13)	

Bold font represents significant p-value.
Mm = millimeter.
$Unclear why percentage missing is so high.
[a] Missing not included in analyses based on relatively small group.
[b] History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
[c] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

ablation, type of hospital where treatment took place which was either a tertiary referral centre (i.e. academic centre or comprehensive cancer centre) or regional hospital and annual oncological network volume. Major liver resection was defined as resection of three or more adjacent Couinaud segments [16].

2.4. Statistical analysis

Mean percentage and upper and lower limits of separate factors in all oncological networks was calculated to assess variation between oncological networks. The significance of these differences in factors between oncological networks was assessed using univariable logistic regression models. Differences between oncological networks were assessed also grouped by oncological network size as differences might be attributable to the size of oncological networks. Oncological networks were categorized in low procedural volume (<500 resections), middle procedural volume (500–1000 resections) and high procedural volume (>1000 resections).

Association of case-mix factors with outcomes was assessed using multivariable logistic regression. Case-mix factors were included in multivariable analysis based on the p-value observed in univariable logistic regression ($p < 0.10$). Restriction of the multivariable logistic regression model was needed due to the number of degrees of freedom in the model for mortality due to low number of events.

To visualize differences in 30-day major morbidity and 30-day mortality, uncorrected funnel plots were created. These funnel plots show the number of patients treated in an oncological network compared to the mean number of events in the same oncological network. This is plotted and compared to the mean number of events of all included patients. If an oncological network is above the mean outcome of all included patients, the oncological network performs worse compared to other oncological networks. If an oncological network is under the mean outcome, it performs better than average. Also, 95% confidence intervals are created on the basis of the mean outcomes and total included patients indicating statistical significance of outliers.

In case-mix corrected funnel plots, the observed/expected ratio (O/E ratio) was used to assess differences between oncological networks. Using multivariable logistic regression, expected 30-day morbidity and 30-day mortality was calculated per patient. All patients in an oncological network together compose the expected morbidity and mortality per oncological network. By dividing the observed morbidity of every oncological network by the expected morbidity of that oncological network, the O/E ratio was calculated. An O/E ratio above 1 indicated that an oncological network performed worse than expected, an O/E ratio below 1 indicated that an oncological network performed better than expected. The 95% confidence intervals (CI) were calculated to indicate whether the O/E ratio of an oncological network was statistically different compared to the average O/E ratio of all oncological networks together. All plots were compared between on a hospital level and an oncological network level.

Multicollinearity in multivariable models was tested using the Variance Inflation Factor (VIF). A VIF of 3 was the cut-off value indicating multicollinearity and if so, one variable was excluded of the analysis. Patients with missing values were analysed as a separate group in multivariable logistic regression if these exceeded 5% of the total included number of patients. If the missing values in a variable was below 5%, the missing patients were excluded from the analysis.

All analyses were performed in R version 3.2.2® (R Core Team (2018): A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

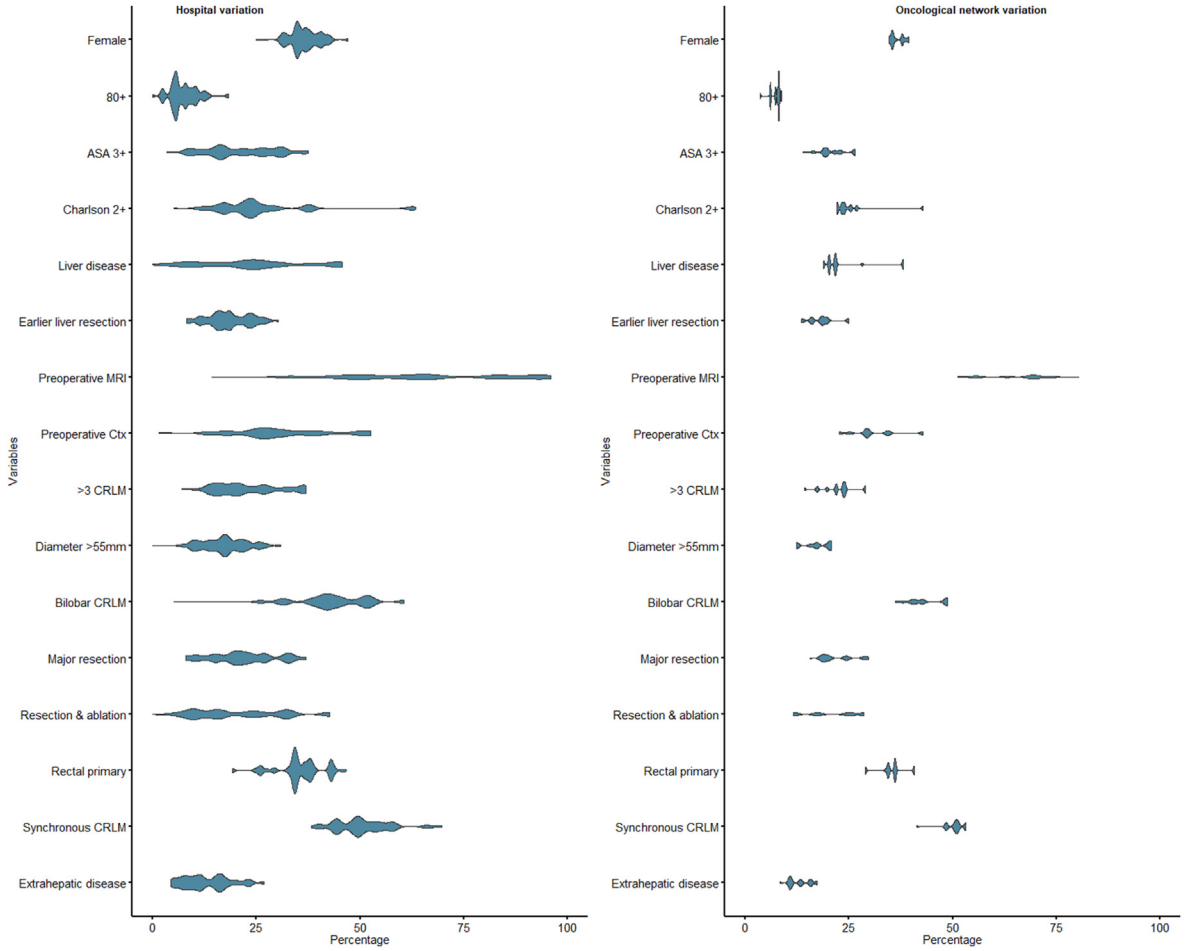

Fig. 2. a&b. Violin graph showing the distribution of mean percentages (range) of case-mix variables per hospital and per oncological network in the Netherlands in patients who underwent liver resection for colorectal liver metastases between 2014 and 2019.

3. Results

In total 5383 patients who underwent liver resection for CRLM in the Netherlands were included from 28 hospitals together assembling 7 oncological networks. Oncological networks were different in size with the largest oncological network treating 1189 patients and the smallest treating 226 patients during the study period (Table 1). Overall 30-day major morbidity was 5.7% and 30-day mortality was 1.5%. Different collaboration agreements regarding preoperative workup and treatment of CRLM were observed between oncological networks (Supplementary Table 1).

3.1. Between-hospital and oncological network variation

Differences in patient characteristics between hospitals were observed for age (80 years or older, 0.0%–18.2%, $p < 0.001$), CCI (2 or higher, 5.0%–63.3%, $p < 0.001$), ASA classification (3 or higher, 3.3%–37.4%, $p < 0.001$), history of liver resection (8.1%–30.3%, $p < 0.001$), liver disease (0.0%–45.6%, $p < 0.001$), use of preoperative MRI (14.3%–96.0%, $p < 0.001$) and use of preoperative chemotherapy (1.5%–52.6%, $p < 0.001$). Variation in tumour characteristics between hospitals included: number of metastases (3 or more CRLM, 7.0–37.0, $p < 0.001$), maximum diameter of largest CRLM prior to treatment of 55 mm (0.0–30.8, $p < 0.001$), use of combined resection and ablation (0.0%–42.7%, $p < 0.001$), major liver resection performed (7.0%–37.0%, $p < 0.001$), rectal primary tumour (19.1%–46.6%, $p < 0.001$), bilobar disease (5.0%–60.6%, $p < 0.001$), and extrahepatic disease (4.4%–26.9%, $p < 0.001$) (Fig. 2a & Supplementary Table 2a).

Differences in patient and tumour characteristics between oncological networks were smaller as compared to hospital variation in case-mix factors. Differences regarding patient characteristics were observed with regard to CCI (2 or higher, 22.1%–42.3%, $p < 0.001$), ASA classification (3 or higher, 13.9%–26.4%, $p < 0.001$), history of liver resection (13.5%–24.9%, $p < 0.001$), liver disease (18.8%–38.0%, $p < 0.001$), use of preoperative MRI (51.2%–80.4%, $p < 0.001$) and use of preoperative chemotherapy (22.7%–42.8%, $p < 0.001$). Variation in tumour characteristics observed between oncological networks included: number of metastases (3 or more CRLM, 14.3%–28.9%, $p < 0.001$), maximum diameter of largest CRLM prior to treatment of 55 mm (12.4%–20.6%, $p < 0.001$), use of combined resection and ablation (11.8%–28.5%, $p < 0.001$), major liver resection performed (15.5%–29.7%, $p < 0.001$), rectal primary tumour (28.9%–40.7%, $p = 0.002$), bilobar disease (36.2%–48.7%, $p < 0.001$), and extrahepatic disease (8.4%–17.3%, $p < 0.001$) (Fig. 2b, Supplementary Table 2b). Other case-mix factors were not different between oncological networks.

3.2. Factors associated with 30-day major morbidity and 30-day mortality

Factors associated with 30-day major morbidity included sex

Table 2a
Univariable and multivariable logistic regression model to assess the association of patient and tumour characteristics with 30-day major morbidity in patients with colorectal liver metastasis (CRLM) in the Netherlands between 2014 and 2019.

			Univariable analysis			Multivariable analysis		
Factor		N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex					<0.001			**0.003**
	Male	3405	1			1		
	Female	1963	0.64	0.49–0.82		0.64	0.48–0.86	
	Missing*	15						
Age in years					0.012			**0.039**
	<50	386	1			1		
	50–64	1871	1.88	1.05–3.76	0.050	1.60	0.88–3.22	0.154
	65–79	2722	2.26	1.27–4.45	0.010	1.79	0.99–3.59	0.072
	≥80	395	2.70	1.37–5.72	0.006	2.31	1.12–5.07	**0.028**
	Missing*	9						
Charlson Comorbidity Index (CCI)					0.079			0.519
	0/1	4016	1			1		
	≥2	1367	1.25	0.97–1.61		1.09	0.82–1.45	
Body Mass Index			1.00	0.97–1.02	0.715	1.01	0.98–1.01	0.623
American Society of Anesthesiology (ASA) classification					<0.001			**0.015**
	I/II	4152	1			1		
	III +	1107	1.57	1.20–2.03		1.44	1.07–1.91	
	Missing*	124						
Histopathology liver parenchyma§					0.116			0.368
	Normal liver	3467	1			1		
	Steatosis	856	1.36	1.01–1.82	0.042	1.33	0.96–1.91	0.081
	Steato-hepatitis	86	1.55	0.64–3.17	0.278	1.70	0.70–3.56	0.196
	Cirrhosis	41	1.38	0.33–3.85	0.597	0.50	0.03–2.39	0.499
	Sinusoidal dilatation	57	2.05	0.78–4.48	0.101	1.49	0.50–3.60	0.416
	Missing	876	0.86	0.60–1.20	0.380	0.98	0.65–3.56	0.924
History of liver resection					0.469			0.422
	No	4299	1			1		
	Yes	975	1.11	0.83–1.48		1.36	0.63–2.78	
	Missing*	109						
History of preoperative chemotherapy					0.855			0.763
	No	3480	1			1		
	Yes	1563	1.04	0.80–1.34	0.756	1.01	0.82–1.41	0.652
	Missing	340	1.11	0.68–1.72	0.663	1.03	0.71–1.74	0.813
Number of lesions					0.697			0.368
	1	2302	1			1		
	2	1113	0.89	0.64–1.21	0.458	1.09	0.78–1.53	0.625
	3	580	1.17	0.80–1.69	0.406	1.16	0.78–1.71	0.456
	4	372	0.85	0.50–1.37	0.527	1.35	0.87–2.06	0.172
	≥5	798	1.05	0.73–1.46	0.799	1.31	0.82–2.03	0.243
	Missing*	218						
Maximum diameter largest CRLM (mm)*					0.007			0.638
	<20	1445	1			1		
	20–34	1727	1.12	0.81–1.56	0.491	0.77	0.54–1.11	0.166
	35–54	899	1.41	0.98–2.04	0.062	1.12	0.70–1.51	0.713
	≥55	549	2.00	1.36–2.94	<0.001	1.54	0.84–1.97	0.099
	Missing	763	1.40	0.95–2.05	0.083	0.75	0.48–1.15	0.190
Major liver resection					<0.001			**<0.001**
	No	4204	1			1		
	Yes	1179	2.06	1.61–2.62		1.98	1.49–2.62	
Bilobar disease					0.982			0.802
	No	2963	1			1		
	Yes	2259	1.00	0.79–1.26		1.04	0.77–1.41	
	Missing*	161						
Location primary tumour					0.005			**0.024**
	Colon	3470	1			1		
	Rectal	1898	0.70	0.54–0.90		0.73	0.55–0.96	
	Missing*	15						
Type of metastasis					0.010			
	Metachronous	2145	1					
	Synchronous	2182	1.48	1.15–1.93	0.003			
	Missing	1056	1.15	0.82–1.61	0.398			
Extrahepatic disease					0.122			0.267
	No	4423	1			1		
	Yes	658	1.22	0.87–1.68	0.235	1.34	0.93–1.88	0.102
	Missing	302	0.63	0.32–1.11	0.139	0.91	0.34–2.00	0.836
Type of hospital[1]					0.145			0.263
	Regional	2952	1			1		
	Tertiary referral centres	2431	1.19	0.94–1.49		1.15	0.90–1.50	

Bold font represents significant p-value.
Mm = millimeter.
$ Unclear why percentage missing is so high.

(female, aOR 0.64, CI 0.48–0.86, p = 0.003), age (80 or higher aOR 2.31, CI 1.12–5.07, p = 0.028), ASA classification (3 or higher aOR 1.44, CI 1.07–1.91, p = 0.015), major liver resection (aOR 1.98, CI 1.49–2.62, p < 0.001), rectal primary tumour (aOR 0.73, CI 0.55–0.96, p = 0.024), and synchronous metastases (aOR 1.84, CI 1.38–2.47, p < 0.001) (Table 2a).

Factors associated with 30-day mortality included age of 80 or higher (aOR 9.32, CI 1.66–1.75, p = 0.037), ASA classification of 3 or higher (aOR 3.61, CI 2.27–5.75, p > 0.001), histological steatohepatitis (aOR 4.66, CI 1.32–12.7, p = 0.006), histological sinusoidal dilatation (aOR 4.08, CI 1.08–12.1, p = 0.020), history of liver resection (aOR 2.00, CI 1.19–3.26, p = 0.007), and major liver resection (aOR 5.80, CI 3.58–9.52, p < 0.001) (Table 2b).

Multicollinearity was assessed in all models and synchronous metastases was excluded from the statistical model for 30-day major morbidity due to multicollinearity with previous liver surgery.

3.3. Comparison of 30-day major morbidity and 30-day mortality on hospital and oncological network level

Uncorrected 30-day major morbidity ranged between 3.3% and 13.1% for hospitals (Fig. 3a). Uncorrected 30-day mortality ranged between 0.0% and 4.5% for hospitals (Fig. 4a). Expected 30-day morbidity between hospitals ranged between 4.8% and 6.9%. Expected 30-day mortality between hospitals ranged between 0.9% and 3.1%. After case-mix correction, variation between hospitals in both outcomes was observed with a few positive outliers (Fig. 5a & Fig. 6a).

Uncorrected 30-day major morbidity ranged between 4.4% and 6.0% for oncological networks (Fig. 3b). Uncorrected 30-day mortality ranged between 0.0% and 2.5% (Fig. 4b). Expected 30-day major morbidity ranged between 5.5% and 6.0% between oncological networks and expected 30-day mortality ranged between 1.0% and 2.2%. After case-mix correction, variation between oncological networks in both outcomes was observed but this variation was smaller as compared to comparison on a hospital level (Figs. 5b and 6b).

3.4. Variation case-mix and outcomes in high procedural oncological networks

In the three largest oncological networks differences in case-mix variables observed included ASA classification (3 or higher 19.0%–26.4%, p < 0.001), use of preoperative MRI (55.6%–70.1%, p < 0.001), use of preoperative chemotherapy (29.2%–34.4%, p = 0.014), size of largest CRLM (maximum diameter prior to treatment of 55 mm 12.4%–20.3%, p < 0.001), bilobar disease (40.7%–48.9%, p < 0.001), extrahepatic disease (10.7%–15.7%, p < 0.001), combined resection and ablation (17.2%–28.5%, p < 0.001) and major liver resection performed (18.4%–24.3%, p = 0.002).

Uncorrected 30-day morbidity ranged between 7.0% and 9.2% between these large oncological networks and uncorrected 30-day mortality ranged between 1.2% and 1.8%. Expected 30-day morbidity ranged between 5.5% and 5.8% between these large oncological networks and expected 30-day mortality ranged between 1.4% and 1.7%.

4. Discussion

This study is the first to describe nationwide oncological network formation, and to assess differences in patient demographics, disease burden and postoperative outcomes between oncological networks for CRLM surgery. Collaboration of hospitals within oncological networks has been initiated in the Netherlands to decrease variation in clinical practice and to improve outcomes. Differences in patient demographics, disease burden and treatment characteristics were observed between oncological networks and reflects current variation in workup and treatment between Dutch oncological networks. However, variability between oncological networks regarding case-mix and outcomes was considerably smaller as compared to between-hospital variation. This results from procedural volumes of oncological networks, topographical orientation of oncological networks and inclusion of at least one tertiary referral centre and several regional hospitals in every oncological network. Therefore, comparing outcomes and auditing on an oncological network level should be pursued instead of on a hospital level as a result of differences in type of care delivered in the hospitals performing liver surgery.

Oncological networks were formed during centralization of surgery in the Netherlands to create referral patterns within oncological networks resulting in decreased variation in preoperative assessment, operative treatment and outcomes [12,17,18]. Due to centralization of liver surgery, differences between hospitals have increased as more complex cases are referred to tertiary centres while regional hospitals perform less complex resections as has been shown previously [19,20]. For this reason, it is harder to compare quality of care on a hospital level as variation in treatment plans is present between hepatobiliary specialists and probability of resection depends on outcomes of MDT meetings [9,21–29]. In this study, variation in case-mix and outcomes existed on an oncological network level but was much smaller as compared to on a hospital level. This might be a result of inconsistencies that exist between oncological networks regarding criteria of resectability and differences in therapeutic strategies regarding CRLM [21,23]. However, formation of oncological networks has improved collaboration of hospitals in oncological networks and decreases variability in case-mix and outcomes between oncological networks. This is a result of specific tertiary care which is delivered in high specialty centres. For this reason, comparing quality of care should be pursued on an oncological network level as differences between oncological networks are smaller due to inclusion of at least one tertiary referral centre and several regional hospitals.

Although differences in case-mix exist between oncological networks, influence of several case-mix factors on 30-day major morbidity and 30-day mortality were comparable to an earlier study regarding use of case-mix correction to compare hospital performances using data from the DHBA [12]. However, differences in case-mix factors and expected outcomes between oncological networks as observed in the current study are smaller compared to differences between hospitals [12]. Differences in uncorrected and expected outcomes are the main reason for case-mix correction as the difference between observed and expected outcomes is a result of factors that cannot be influenced by the surgical team [12,17,18]. The authors hypothesize that due to the procedural volume in oncological networks as well as inclusion of both tertiary referral centres and regional hospitals from a specific topographical region differences in case-mix play a minor role in comparing outcomes

[*] Missing not included in analyses based on relatively small group.
[§] History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
[1] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

Table 2b
Univariable and multivariable logistic regression model to assess the association of patient and tumour characteristics with 30-day mortality in patients with colorectal liver metastasis (CRLM) in the Netherlands between 2014 and 2019.

			Univariable analysis			Multivariable analysis		
Factor		N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex					0.047			0.120
	Male	3405	1			1		
	Female	1963	0.60	0.36–0.98		0.66	0.39–1.10	
	Missing*	15						
Age in years					0.006			**0.014**
	<50	386	1			1		
	50–64	1871	4.16	0.86–74.8	0.165	4.14	0.84–74.8	0.169
	65–79	2722	7.35	1.61–130	0.049	6.97	1.48–125	0.057
	≥80	395	8.98	1.68–165	0.038	9.32	1.66–175	**0.037**
	Missing*	9						
Charlson Comorbidity Index (CCI)					0.713			
	0/1	4016	1					
	≥2	1367	1.10	0.66–1.77				
Body Mass Index			1.03	0.99–1.08	0.144			
American Society of Anesthesiology (ASA) classification					<0.001			**<0.001**
	I/II	4152	1			1		
	III +	1107	4.16	2.67–6.48		3.61	2.27–5.75	
	Missing*	1234						
Histopathology liver parenchyma§					0.013			**0.043**
	Normal liver	3467	1			1		
	Steatosis	856	1.52	0.83–2.65	0.158	1.41	0.75–2.52	0.259
	Steato-hepatitis	86	3.88	1.15–9.88	0.011	4.66	1.32–12.7	**0.006**
	Cirrhosis	41	4.08	0.65–13.9	0.058	3.79	0.55–15.1	0.099
	Sinusoidal dilatation	57	6.01	1.76–15.5	<0.001	4.08	1.08–12.1	**0.020**
	Missing	876	1.11	0.56–2.04	0.759	1.16	0.56–2.21	0.676
History of liver resection					0.002			**0.007**
	No	4299	1			1		
	Yes	975	2.11	1.30–3.35		2.00	1.19–3.26	
	Missing*	109						
History of preoperative chemotherapy					0.024			0.292
	No	3480	1			1		
	Yes	1563	1.42	0.89–2.22	0.132	1.10	0.67–1.80	0.697
	Missing	340	0.21	0.01–0.95	0.049	0.30	0.02–1.40	0.235
Number of CRLM					0.107			
	1	2302	1					
	2	1113	1.20	0.62–2.24	0.584			
	3	580	2.01	1.00–3.85	0.042			
	4	372	0.71	0.17–2.03	0.579			
	≥5	798	2.02	1.08 0 3.68	0.023			
	Missing*	218						
Maximum diameter largest CRLM (mm)*					0.009			0.222
	<20	1445	1			1		
	20–34	1727	2.02	0.99–4.44	0.062	1.76	0.85–3.93	0.145
	35–54	899	2.93	1.37–6.63	0.007	2.05	0.93–4.75	0.078
	≥55	549	3.48	1.52–8.20	0.003	1.69	0.70–4.19	0.243
	Missing	763	3.07	1.41–7.05	0.006	2.56	1.12–6.06	**0.027**
Major liver resection					<0.001			**<0.001**
	No	4204	1			1		
	Yes	1179	5.96	3.81–9.47		5.80	3.58–9.52	
Bilobar disease					0.184			
	No	2963	1					
	Yes	2259	1.35	0.87–2.11				
	Missing*	161						
Location primary tumour					0.395			
	Colon	3470	1					
	Rectal	1898	0.81	0.50–1.30				
	Missing*	15						
Type of metastasis					0.379			
	Metachronous	2145	1					
	Synchronous	2182	0.98	0.59–1.64	0.947			
	Missing	1056	1.43	0.80–2.50	0.212			
Extrahepatic disease					0.752			
	No	4423	1					
	Yes	658	1.27	0.65–2.27	0.459			
	Missing	302	1.15	0.40–2.60	0.770			
Type of hospital[1]					0.321			
	Regional	2952	1					
	Tertiary referral centres	2431	1.25	0.80–1.94				

Bold font represents significant p-value.
Mm = millimeter.
$ Unclear why percentage missing is so high.

* Missing not included in analyses based on relatively small group.
§ History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
[1] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

between oncological networks. Centralization and formation of oncological networks has decreased variation in practice and outcomes on an oncological network level compared to on a hospital level. However, variation is still present. Therefore, collaboration of hospitals within oncological networks and between oncological networks should be intensified to further equalize quality of care between oncological networks.

The authors' perspective for the future of these oncological networks includes a more intensive collaboration of hospitals within oncological networks using best practice guidelines for preoperative screening and interventions to optimize modifiable risk factors. Current variation regarding collaboration agreements within Dutch oncological networks is present and has been described by differences in case-mix and treatment strategies in the Dutch oncological networks. Intensifying collaboration of hospitals within oncological networks based on strict best practice nationwide guidelines will address and decrease practice variation in treatment strategies between oncological networks. As a result, all oncological networks will provide care for CRLM patients according nationwide guidelines on preoperative workup and treatment thus providing equal quality of care in every oncological network independent of the oncological network where treatment takes place. Important reasons to decrease the observed practice variation are the associated better outcomes for patients and lower costs [4,30,31]. From an auditing perspective, comparing outcomes between oncological networks instead of between hospitals can be more valuable as the influence of confounding factors is smaller as compared to comparing quality of care on a hospital level. This is particularly true for high procedural oncological networks. In the authors opinion, striving for comparable oncological networks regarding procedural volume will make comparison of outcomes more valid as influence of case-mix is decreasing as procedural volume increase. As a result, patients will receive comparable quality of care and possibilities regarding outcomes will be equal and will not depend on the oncological network where the patient is treated. This study can be used for formation and comparison of oncological networks in several oncological surgical fields as this is the first to referral patterns of specialized oncological care on a nationwide basis.

Limitations of this study include lacking of 90-day postoperative outcomes which have shown to be a better estimate of postoperative outcomes compared to 30-day postoperative outcomes [32]. Technical complexity of the procedure and several other factors that might be thought of as case-mix factors were not retrievable as this study was performed from an auditing database. Type of hospital was included in the case-mix model as this reflects complexity of procedures of which data was not available in the DHBA [12]. Future studies on oncological networks should also include variation in oncological outcomes of CRLM patients to assess which case-mix factors influence disease-free survival, overall survival and compare oncological networks on these outcomes. To date, no long-term oncological outcomes are available in

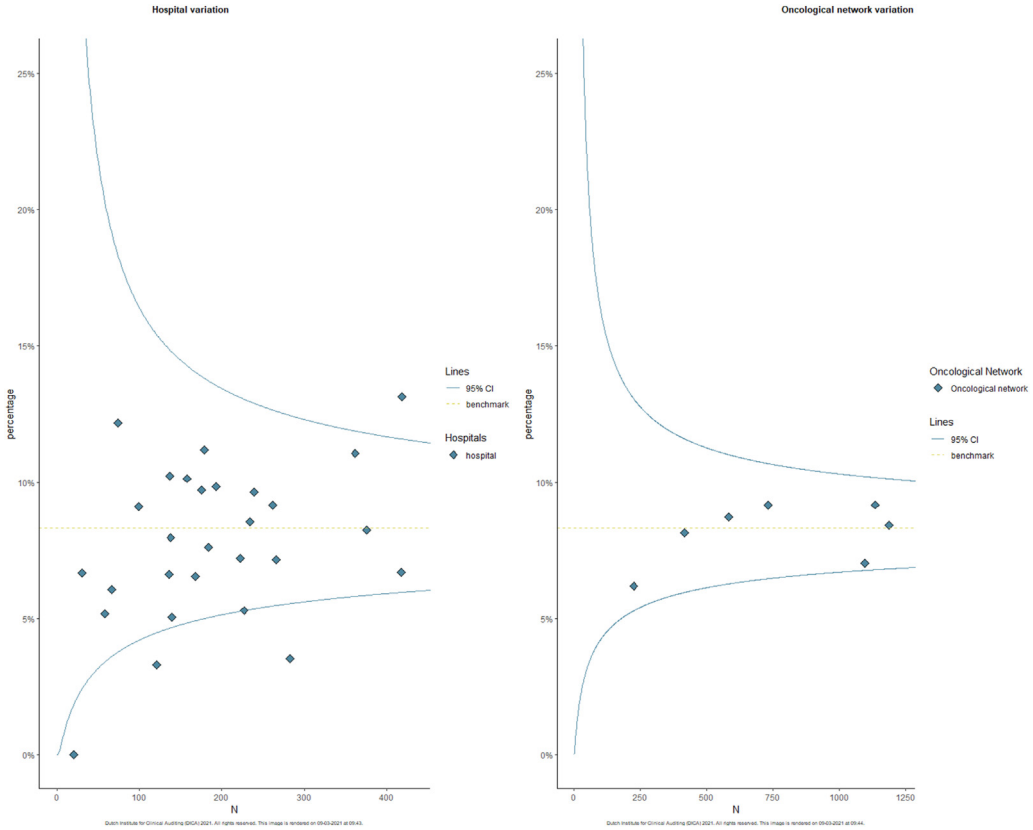

Fig. 3. a&b. Uncorrected funnel plot of between-hospital and between oncological-network variation in 30-day major morbidity in patients with colorectal liver metastases in the Netherlands between 2014 and 2019.

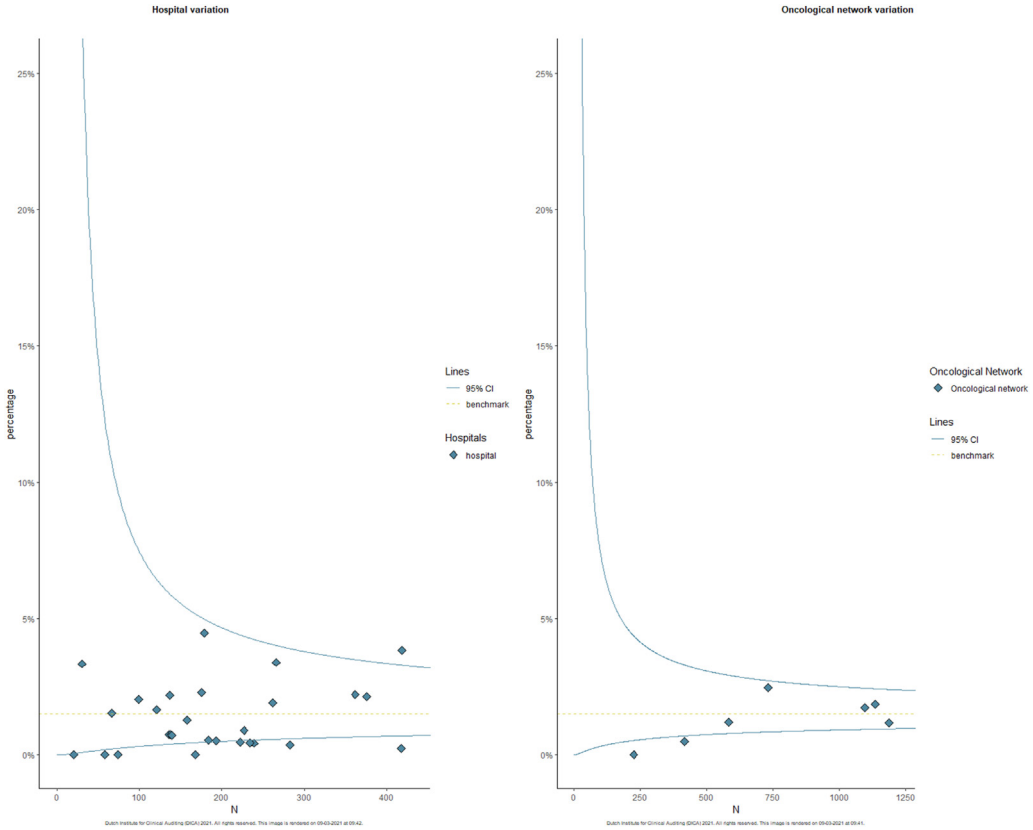

Fig. 4. a&b. Uncorrected funnel plot of between-hospital and between oncological-network variation in 30-day mortality in patients with colorectal liver metastases in the Netherlands between 2014 and 2019.

the DHBA.

In conclusion, this study shows that patient demographics, disease burden, therapeutic strategies and surgical outcomes are different between oncological networks consisting of tertiary care centres and regional hospitals from a topographical region in the Netherlands. This reflects that differences in workup and treatment of CRLM is still present between oncological networks the Netherlands. However, the observed variation is much smaller as compared to between-hospital variation. This underlines that auditing and measuring quality of care should be pursued on an oncological network level rather than on a hospital level. To further decrease variation between oncological network, nationwide agreements regarding preoperative and operative treatment of CRLM should be focused on as well as intensifying collaboration of hospitals within oncological networks. Ultimately, the objective is that treatment of patients will be independent of the oncological network where they receive treatment.

Author contribution

AE: Conceptualization, Funding acquisition, Formal analysis, Writing – original draft, Writing – review & editing, Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review. NK: Conceptualization, Funding acquisition, Formal analysis, Writing – original draft, Writing – review & editing, Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review. MW: Conceptualization, Formal analysis, Study concepts, Study design, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis. DG: Conceptualization, Formal analysis, Study concepts, Study design, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis. JK: Conceptualization, Formal analysis, Study concepts, Study design, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis. RS. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. MD. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. PB. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. HH. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. WR. Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. GP. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. WL. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. DL. Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. NA: Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. CV: Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. KK. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. CB. Funding acquisition,

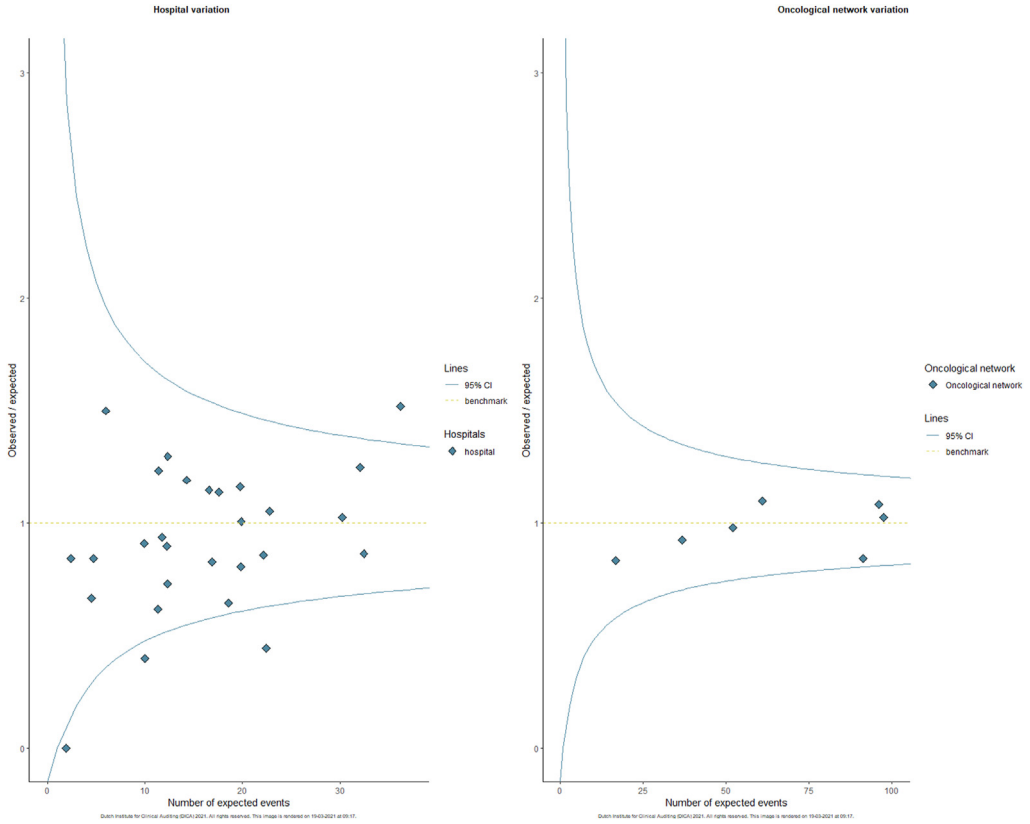

Fig. 5. a&b. Case-mix corrected funnel plot of between-hospital and between oncological-network variation in 30-day major morbidity in patients with colorectal liver metastases in the Netherlands between 2014 and 2019.

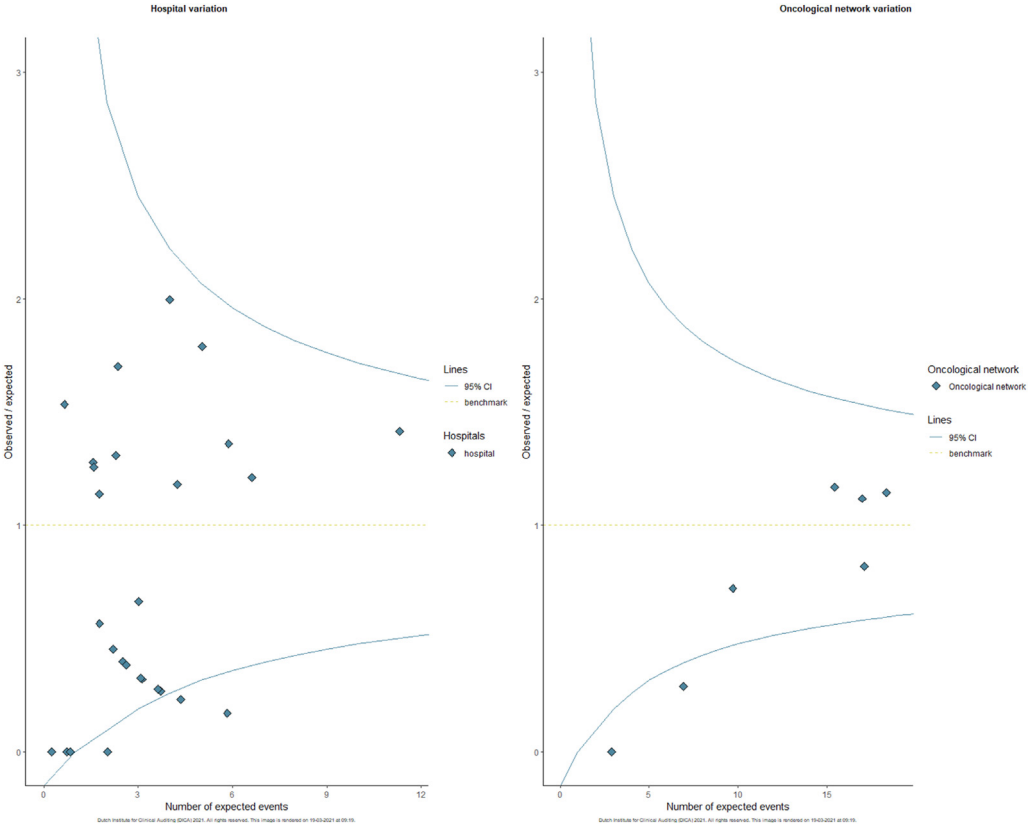

Fig. 6. a&b. Case-mix corrected funnel plot of between-hospital and between oncological-network variation in 30-day mortality in patients with colorectal liver metastases in the Netherlands between 2014 and 2019.

Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. KB: Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. EB. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. MV: Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. NH. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. SO. Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. HT: Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. HE. Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. EC. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. HM. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. GK: Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. MW. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. DG. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review. JK. Funding acquisition, Writing – original draft, Writing – review & editing, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to thank all surgeons, interventional radiologists and administrative nurses for data registration in the DHBA database, as well as the Dutch Hepato Biliary Audit Group for scientific input.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.09.004.

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