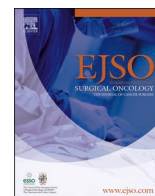


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## Association of modified textbook outcome and overall survival after surgery for colorectal liver metastases: A nationwide analysis

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### ABSTRACT

**Background:** Textbook outcome (TO) represents a multidimensional quality measurement, encompassing the desirable short-term outcomes following surgery. This study aimed to investigate whether achieving TO after resection of colorectal liver metastases (CRLM) surgery is related to better overall survival (OS) in a national cohort.

**Method:** Data was retrieved from the Dutch Hepato Biliary Audit. A modified definition of TO (mTO) was used because readmissions were only recorded from 2019. mTO was achieved when no severe postoperative complications, mortality, prolonged length of hospital stay, occurred and when adequate surgical resection margins were obtained. To compare outcomes of patients with and without mTO and reduce baseline differences between both groups propensity score matching (PSM) was used for patients operated on between 2014 and 2018.

**Results:** Out of 6525 eligible patients, 81 % achieved mTO. For the cohort between 2014 and 2018, those achieving mTO had a 5-year OS of 46.7 % (CI 44.8–48.6) while non-mTO patients had a 5-year OS of 33.7 % (CI 29.8–38.2),  $p < 0.001$ . Not achieving mTO was associated with a worse OS (aHR 1.34 (95 % CI 1.17–1.53),  $p$

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< 0.001. Median follow-up was 76 months., PSM assigned 519 patients to each group. In the PSM cohort patients achieving mTO, 5-year OS was 43.6 % (95 % CI 39.2–48.5) compared to 36.4 % (95 % CI 31.9–41.2) in patients who did not achieve mTO,  $p = 0.006$ .

**Conclusion:** Achieving mTO is associated with improved long-term survival. This emphasizes the importance of optimising perioperative care and reducing post-operative complications in surgical treatment of CRLM.

## 1. Introduction

Textbook outcome (TO) represents a multidimensional quality measurement, encompassing the desirable short-term outcomes following surgery. By meeting all pre-defined requirements, this comprehensive measure provides a broader reflection of the quality of care, surpassing the limitations of single outcome indicators [1–3].

In various surgical fields, TO has been thoroughly evaluated and proven a reliable parameter for assessing short-term outcomes. By aiding in the evaluation of care for surgical patients, TO has the potential to improve healthcare processes, ultimately benefiting patients and leading to improved survival rates [4–11].

A recent single-centre study has revealed that patients who undergo surgery for colorectal liver metastases (CRLM) and achieve TO experience improved 5-year survival rates compared to those who do not achieve this outcome [12]. Considering the limited focus of this study in just one academic hospital, we could gain a better understanding of the association between TO and CRLM surgery in a nationwide cohort study. Since 2014, all patients undergoing liver resection in the Netherlands have been recorded in the Dutch Hepato Biliary Audit (DHBA) [13]. Previous research using DHBA data has demonstrated that TO can be employed to evaluate short-term outcomes following liver surgery [14].

The aim of this study was to investigate whether achieving TO after CRLM surgery was related to better survival in a national cohort.

## 2. Methods

The study was approved by the DHBA Scientific Committee. Under the Dutch law, no ethical approval or informed consent was needed since data is handled anonymously.

### 2.1. Patients

All patients above the age of 18 and who underwent liver surgery for CRLM between the 1st of January 2014 and 31<sup>st</sup> December 2022 were included. Patients with missing essential data (data of surgery, date of birth or unknown origin of tumour) were excluded. Patients with a history of liver resection or treated with thermal ablation alone were also excluded from analysis.

### 2.2. Dataset

This nationwide, population-based study was performed using data from the DHBA registry and the national insurance database (Vektis). The DHBA is a mandatory registry including all patients who underwent liver surgery and/or thermal ablation. In 2017, data verification of the DHBA was performed. The DHBA did not provide sufficient data on long-term outcomes, therefore the DHBA was linked to Vektis. Linking both datasets was based on personal security numbers, linking process has been described before [15]. Due to the General Data Protection Regulation, linkage was only sufficient between 2014 and 2018. Linkage between 2014 and 2018 was 86 %. Patients who could not be linked were evenly distributed among those who achieve and those who did not achieve mTO.

### 2.3. Modified textbook outcome

The original definition of TO, used as quality indicator in the DHBA consists of the absence of severe postoperative complications (Clavien-

Dindo grade 3a or higher), mortality, readmission within 30 days after surgery, or prolonged length of stay (LOS), defined as LOS > p90 which corresponds with 14 days or longer, and obtaining surgical resection margins R0 and R1 [14]. For this manuscript R0 (microscopically negative) or R1 (microscopic residual tumour located <1 mm at resection margin) were considered adequate surgical resection margins.

Readmissions have only been registered in the DHBA since 2019. Therefore, we needed to adjust the definition of TO. Patients achieved modified Textbook Outcome (mTO) when there was an absence of severe postoperative complications, mortality, and LOS was not prolonged, and a surgical resection margin R0/R1 were obtained. Presumably, due to this modification an overestimation of patients who achieve mTO is made.

### 2.4. Outcome

The primary outcome of this study was overall survival (OS) in patients who achieved and did not achieve mTO. Secondary outcomes were the factors associated with OS.

### 2.5. Variables for analysis

The following patient, tumour and treatment characteristics were used for analysis; sex, age, Charlson Comorbidity Index (CCI), American Society of Anaesthesiologist (ASA) grade, body mass index (BMI), number of CRLM, diameter of largest CRLM before any tumour specific treatment, timing of metastasis (synchronous; diagnosed within 6 months of primary tumour, metachronous; diagnosed at least 6 months after primary tumour), bilobar disease, surgical technique (open vs. laparoscopic), major liver resection (defined as resection of three adjacent Couinaud segments), type of hospital (regional hospital or tertiary referral centre). In the registry location within the colon was not specified (i.e., left-sided, or right-sided).

### 2.6. Statistical analyses

To compare patients with and without mTO descriptive statistics were used. Categorical variables were presented as numbers and proportions and compared using the chi-square test. Continuous variables were presented as median with inter-quartile range (IQR) and compared using the students' t-test if normally distributed, otherwise the Mann-Whitney-U test was used.

Since readmission was only known in the cohort from 2019 to 2022 we performed a subgroup analysis in this cohort to assess the influence of readmission on achievement of TO. In this cohort the difference in patients who achieved TO and mTO was tested, to measure the effect of our mTO to definition.

Overall survival (OS) was assessed in the cohort between 2014 and 2018 and calculated from day of surgery to date of death of any cause. Patients deceased within 30-days after surgery or in-hospital mortality, were excluded from analysis. Kaplan-Meier survival analysis was used to compare the OS in patients who obtained mTO and who did not obtain mTO and were tested using the log-rank test. Univariable and multivariable Cox regression models were used to assess the influence of obtaining mTO on OS. For the multivariable model all possible factors were selected and included after checking for multicollinearity as no restriction was needed due to the high number of events. Missing items below 5 % were excluded from analysis, if 5 % was exceeded items were analysed as separate group. The proportional hazard assumption was

tested using Schoenfeld residuals. To determine the association of each mTO parameter, with exception of 30-day mortality, a separate multivariable Cox proportional hazards regression model was used including severe complications, prolonged LOS and surgical resection margin.

In order to minimize potential imbalances, additional propensity score matching (PSM) was used for patients operated on between 2014 and 2018. For PSM a nearest-neighbour method was used, using a ratio 1:1 with a calliper of 0.2 [16]. For the matching process the following variables were used age at time of surgery, ASA-score, Charlson Comorbidity Index, number of CRLM, diameter of largest CRLM before treatment, presence of extrahepatic metastases and exact on year of surgery. The degree of balance was assessed visually using a Kernel density distribution plot and using standardized mean differences (SMD), a SMD of >0.10 indicated disbalance of this variable between both groups. Additionally, a Kaplan-Meier survival analysis with propensity score matching was conducted to further assess the differences in OS.

All analyses were performed using R version 2023.06.1 (R core Team (2023). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). P values < 0.05 were considered statistically significant.

### 3. Results

In total, 6525 patients including, 5030 (77.1) who underwent liver resection alone and 1495 (22.9 %) patients who underwent combined liver resection and ablation were included in the study. Baseline characteristics are shown in Table 1.

#### 3.1. Modified textbook outcome

Between 2019 and 2022, 2620 patients underwent liver resection, of whom 2117 (81 %) achieved TO and 493 (19 %) did not achieve TO. Of all patients, who did not achieve TO (n = 493), 108 (21 %) did not achieve TO only as a consequence of a readmission. For the achievement of mTO, in this cohort 2226 (85 %) achieved mTO, meaning a potential overestimation of TO versus mTO of 4 %.

In the cohort between 2014 and 2018, 3721 patients were included, of whom 3076 (83 %) achieved mTO. Baseline characteristics of patients who did and did not achieve mTO are shown in Supplementary Table 1.

The most substantial decrease in mTO between 2014 and 2022 was due to severe complications (10 %) and prolonged LOS (12 %) (Supplementary Table 2).

#### 3.2. Overall survival

In patients achieving mTO, 5-year OS was 46.7 % (95%CI 44.8–48.6) compared to 33.7 % (95 % CI 29.8–38.2) in patients who did not achieve mTO, p < 0.001 (Fig. 1). Median follow-up was 76 (IQR 63.9–91.4) months.

Not achieving mTO was associated with a worse OS (aHR 1.34 (95 % CI 1.17–1.53), p < 0.001). Other factors were also associated with worse OS in multivariable cox regression analysis included ASA 3+ score (aHR 1.31 (95 % CI 1.15–1.49), p < 0.001), >1 CRLM (aHR 1.50 (95 % CI 1.31–1.73), p < 0.001), CRLM >5 cm (aHR 1.42 (95 % CI 1.23–1.64), p < 0.001) bilobar disease (aHR 1.16 (95 % CI 1.02–1.32), p = 0.023), data is shown in Table 2.

Individual assessment of parameters of mTO in a multivariable cox regression model, showed prolonged LOS and severe complications were not independently associated with OS, yet surgical resection margin R2 was independently associated with OS (aHR 1.99 (95%CI 1.26–3.14, p = 0.003) (Supplementary Table 3).

mTO was associated with an improved OS in both regional and tertiary referral hospitals (Supplementary Fig. 1).

**Table 1**

Baseline characteristics of patients who underwent liver resection for colorectal liver metastases and achieved or not achieved modified textbook outcome (mTO) between 2014 and 2022 in the Netherlands.

data 2014–2022			
Full cohort			
Factor	No mTO N (%)	mTO N (%)	p-value
	1030	5302	
<b>Sexe</b>			0.3
Male	664 (65)	3315 (63)	
Female	365 (35)	1968 (37)	
Missing	0	18	
<b>Age</b>	68 (59, 75)	66 (58, 74)	<0.001
<b>ASA score</b>			<0.001
ASA 1/2	706 (70)	4115 (78)	
ASA 3+	306 (30)	1150 [22]	
Missing	17	36	
<b>Charlson score</b>			0.006
CCI 0/1	737 (72)	4013 (76)	
CCI 2+	292 (28)	1288 [24]	
<b>Location primary tumour</b>			<0.001
Colon	749 (73)	3418 (65)	
Rectal	279 (27)	1873 (35)	
Missing	1	10	
<b>Timing metastases</b>			<0.001
Metachronous	415 (41)	2541 (50)	
Synchronous	590 (59)	2583 (50)	
Missing	24	177	
<b>Histopathology of liver parenchyma</b>			0.2
Normal liver	676 (66)	3603 (68)	
Steatosis	178 [17]	878 [17]	
Other liver disease	45 (4.4)	166 (3.1)	
Missing	130 [13]	654 [12]	
<b>Number of CRLM</b>			<0.001
1	361 (35)	2208 (42)	
>1	610 (59)	2907 (55)	
Missing	58 (5.6)	186 (3.5)	
<b>Diameter largest CRLM</b>			<0.001
>5 cm	211 [24]	710 [15]	
Missing	135	564	
<b>Bilobar disease</b>	477 (46.3)	2197 (41.4)	0.004
Missing	144 (13.9)	776 (14.6)	
<b>Major liver resection</b>			<0.001
Minor	679 (66)	4326 (82)	
Major	350 (34)	975 [18]	
<b>Preoperative chemotherapy</b>	369 (39)	1578 (31)	<0.001
Missing	71	257	
<b>Tertiary referral centre</b>	504 (49)	2459 (46)	0.13
<b>Textbook Outcome*</b>			<0.001
No TO	1029 (100)	108 (2.0)	
Yes	0 (0)	2132 (40)	
No readmission registered	0 (0)	3061 (58)	

#### 3.3. Propensity score matching

For the cohort between 2014 and 2018 PSM assigned 519 patients to each group. After matching, patient characteristics were well balanced between both groups (Supplementary Table 4).

In the PSM cohort patients achieving mTO, 5-year OS was 43.6 % (95%CI 39.2–48.5) compared to 36.4 % (95%CI 31.9–41.2) in patients who did not achieve mTO, p = 0.006 (Supplementary Fig. 2).

### 4. Discussion

The results of this nationwide study demonstrate that achieving mTO was associated with improved OS when compared to patients who did not achieve mTO. This relevant and profound difference (HR 1.34) was independent of other relevant factors after both multivariate cox analysis and propensity score matching.

A relatively high percentage of patients achieved mTO, however the impact of reaching mTO on OS remains valid. This highlights the

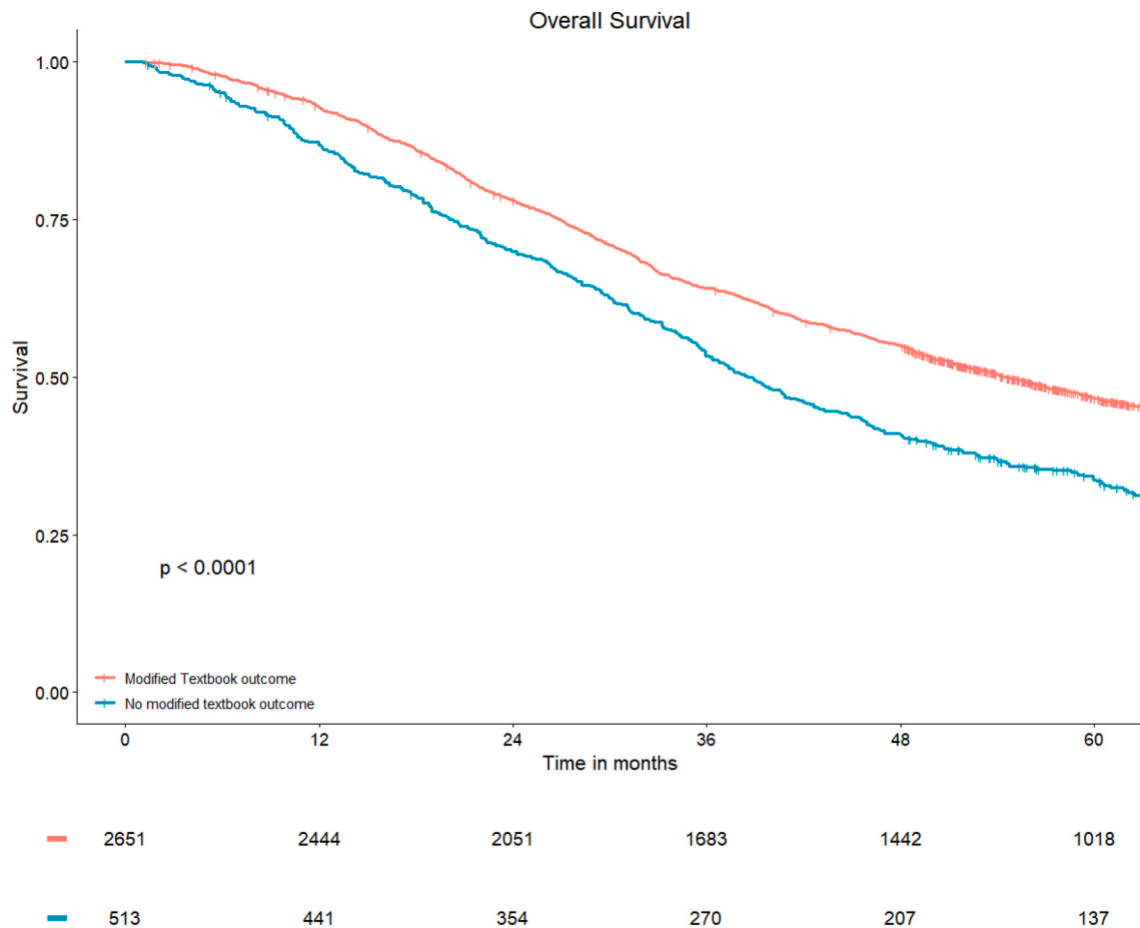


Fig. 1. Kaplan Meier curves estimating overall survival of patients with colorectal liver metastases who underwent liver resection and achieved or did not achieve mTO between 2014 and 2018 in the Netherlands in the unmatched cohort.

**Table 2**  
Multivariable Cox regression analysis of patients who underwent liver resection for colorectal liver metastases between 2014 and 2018 in the Netherlands.

Characteristic	HR	95 % CI	p-value
<b>mTO (no)</b>	1.34	1.17, 1.53	<0.001
<b>Age</b>	1.01	1.01, 1.02	<0.001
<b>ASA score</b>			
ASA 1/2	–	–	
ASA 3+	1.31	1.15, 1.49	0.001
<b>Charlson score</b>			
CCI 0/1	–	–	
CCI 2+	1.12	0.98, 1.26	0.088
<b>Location primary tumour</b>			
Colon	–	–	
Rectal	1.08	0.97, 1.20	0.20
<b>Sexe</b>			
Male	–	–	
Female	0.97	0.87, 1.08	0.6
<b>Timing</b>			
Metachronous	–	–	
Synchronous	1.21	1.09, 1.35	<0.001
>1 CRLM	1.50	1.31, 1.73	<0.001
CRLM >5 cm	1.42	1.23, 1.64	<0.001
Missing	1.20	1.01, 1.42	0.041
<b>Bilobar disease</b>			
Missing	1.16	1.02, 1.32	0.023
Missing	0.87	0.53–1.43	0.6
<b>Major liver resection</b>			
Minor	–	–	
Major	1.04	0.92, 1.18	0.5

HR = Hazard Ratio, CI = Confidence Interval.

importance of the TO definition of the DHBA [14]. In this cohort, a total of 24 hospitals were included, including a diverse range of tertiary referral centres and regional hospitals. Despite the substantial variation in hospital profiles, the association between TO and OS remained statistically significant. Furthermore, when we specifically examined the differences between tertiary and regional hospitals, the difference in OS between mTO and no mTO patients remained significant.

Our analysis also revealed that the achievement of mTO was independent of patient factors indicative of vulnerability, including ASA-score, comorbidities, and patients age, as indicated in the multivariable regression model. Additionally, we used propensity score matching to reduce disbalance in patient characteristics. This finding strongly suggests that the achievement of mTO is primarily dependent on the quality of perioperative care and the management of surgical complications, highlighting the crucial role of the perioperative care pathway. Our findings highlight the importance of optimising peri-operative and intra-operative care pathways to limit the rate of severe surgical complications which may in turn negatively influence survival. This should boost adoption of prehabilitation and Enhanced Recovery After Surgery (ERAS) liver protocols in order to optimise perioperative care pathways in liver surgery. The implementation of ERAS protocols plays an important role in improving outcomes for liver surgery patients [17–19]. ERAS protocols have been associated with a significant reduction in the length of hospital stays and postoperative complications [19]. In addition, as ERAS programmes are designed to reduce the risk of postoperative complications, prehabilitation focusses on enhancing the preoperative physical, nutritional, and psychological aspect of patient’s health to reduce risk of postoperative complications [20]. In patients who underwent liver resection and completed a prehabilitation program

a trend towards less complications were seen [21].

In the coming years, it's predicted that the focus of healthcare will shift towards quality instead of quantity of life. This shift aims to empower healthcare institutions to focus their efforts on improving patient care [22]. In the context of studies following CRLM surgery, most have focused on single factors such as postoperative mortality, postoperative morbidity, and postoperative liver failure, to measure surgical quality [23]. The importance of a reliable quality measure becomes more prominent [24]. mTO serves as a good example of the attributes a quality measure should possess. Additionally, mTO offers increased event rates, improving its ability to detect differences compared to single outcomes. Considering, not all parameters used in mTO were independently associated with OS, proves the advantageous effect of the utilisation of mTO. By integrating information from various aspects of patients' treatment, mTO delivers a clear view of the overall situation. This broad approach detects trends that could be missed if each aspect was considered separately.

Textbook outcome is a composite quality measure. Traditionally TO provides more power to detect differences between hospitals due to its higher event rates. The definition of TO as used in the DHBA was based on previous literature and expert opinion. Relevant parameters were discussed in the scientific committee of the DHBA. Readmissions constitute a relevant quality issue since it could be an adverse consequence for patients and may be related premature discharge. However, its impact seems to be limited, with a potential difference of only 4 %. This is reassuring, even if readmission is not fully covered in the registry, for instance, patients are sometimes readmitted to their original hospital without the reference hospital being informed. This circumstance enhances the usability of our mTO definition on a standardized scale. Moreover, since TO is used for clinical auditing, it is crucial to minimize the registrational burden. The adoption of real-time automated auditing has the potential to bypass the current challenges linked to retrospective data compilation, thus enabling actual insights that are both more precise and promptly available.

It is important to acknowledge the limitations of our study, which stem from its retrospective and audit nature. Long-term follow-up was not mandatory. Unfortunately, 14 % of the follow-up was lost due to the linkage between both datasets. This is caused by the General data protection programme in Europe, and foreign patients or soldiers do not have a social security number [25]. The data of audit registries does not contain detailed information such as recurrences for a disease-free survival analysis. However, Ecker et al. described that the development of recurrent CRLM after liver resection did not reflect non-curability and showed a poor correlation between disease-free survival and overall survival. Additionally, potential issues with the missing readmissions within 30 days after discharge could have influenced the accuracy of our findings.

In conclusion, our nationwide analysis utilising a modified version of TO in patients undergoing liver resection for CRLM reaffirms the association between achieving mTO and improved long-term survival. This highlights the crucial importance of striving to achieve mTO and further underscores the significance of continuous efforts to optimise perioperative care and reduce postoperative complications in CRLM surgery.

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## Conflicts of interest and source of funding

None were declared.

## Data availability statement

Data will be made available upon reasonable request. This paper is presented at the 26th AUGIS & NVGIC annual scientific meeting, in

Oxford.

## 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.

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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.2024.107972>.

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