An integrated view on assuring quality for multimodal therapy in oncologic care

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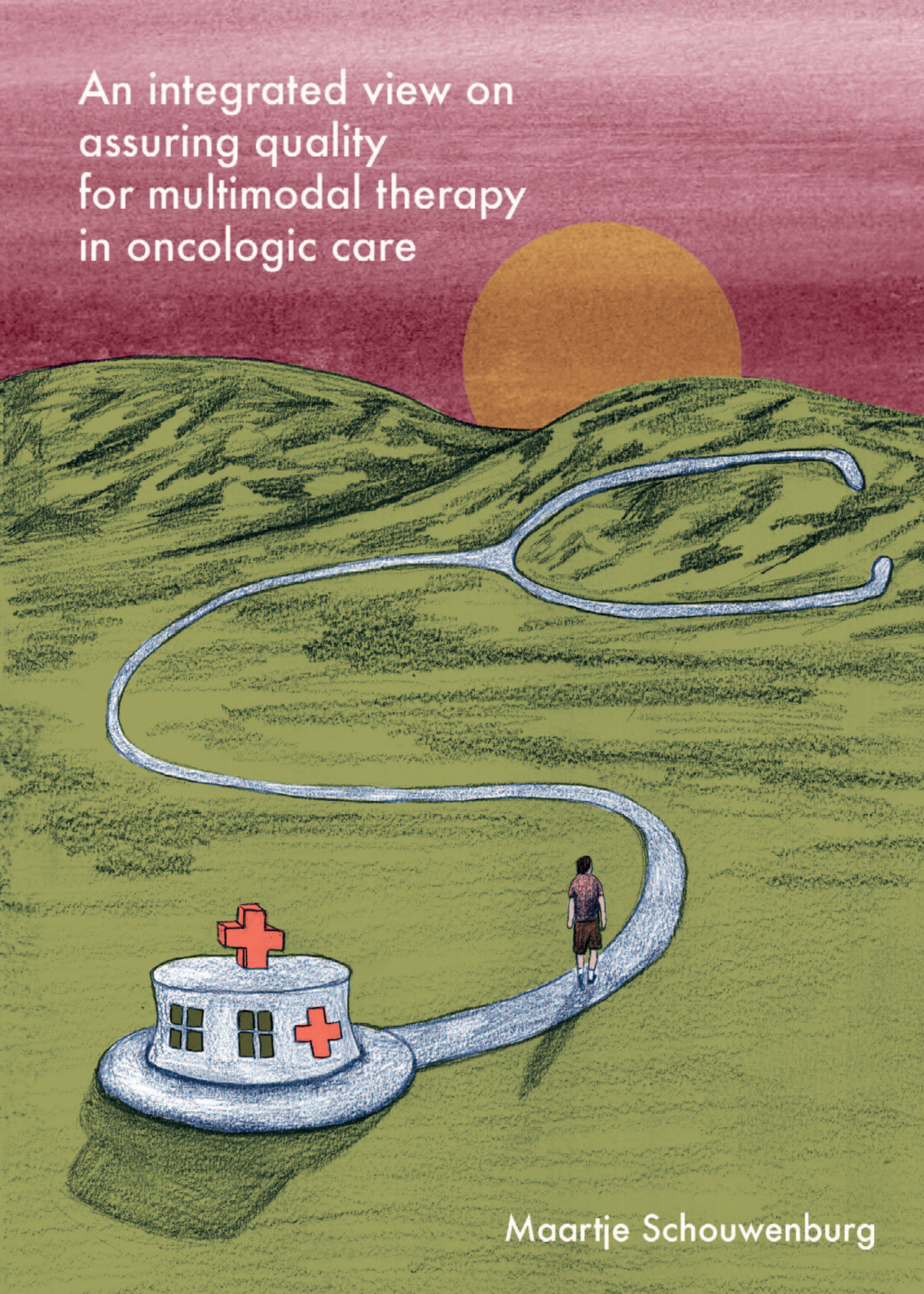

Maartje Schouwenburg

AN INTEGRATED VIEW ON ASSURING QUALITY FOR MULTIMODAL THERAPY IN ONCOLOGIC CARE

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ISBN: 978-94-6361-246-3
Cover design: Jip van den Toorn
Layout and printing: Optima Grafische Communicatie, Rotterdam

This thesis was financially supported by:
Stichting DICA, Universiteitsbibliotheek Leiden, Stichting SBOH

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PROEFSCHRIFT

Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 18 april 2019
klokke 11.15 uur

door

Maartje Gisèle Schouwenburg
Geboren te Leiden in 1987

Promotores:
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Prof. dr. R.A.E.M. Tollenaar

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Leden promotiecommissie:
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CONTENTS

1 General introduction and thesis outline

GENERAL INTRODUCTION

Trends in cancer care

Cancer is still one of the leading causes of morbidity and mortality worldwide. In the Netherlands, the number of cancer deaths remains high mainly due to population growth and aging. In 2017, over 150.000 people died in the Netherlands, with cancer being the most common cause of death (31%), followed by cardiovascular disease (25%) [1].

Fortunately, cancer can increasingly be seen as a chronic disease. Recent advances in the understanding of the molecular profile of tumour cells have led to the promise of precision medicine for treatment of cancer [2]. Novel therapies target key molecules that allow cancer to survive, such as the immune checkpoint inhibitors that inactivate proteins that cancer cells use to evade the immune system, and the targeted therapy that block specific molecules needed for tumour growth and spread. These major advancements have resulted in new promising therapies for patients with advanced cancers of the lung, breast, skin, and kidney previously considered refractory.

Trends in multidisciplinary cancer care

Although surgery is still considered the cornerstone of many cancer treatments, the field of oncologic care becomes more complex with an increase in multimodality therapies. This has motivated the development of multidisciplinary teams, which have been widely adopted in many countries and form an important component in guidelines [3].

In order to assure high-quality multidisciplinary cancer care in The Netherlands, the Dutch federation of oncological societies (SONCOS) has set up multidisciplinary standards listing general and tumour-specific requirements a cancer centre must meet [4]. They include requirements for infrastructure, specialisms that should be available, participation in registration projects and maximum waiting times.

The first SONCOS standardisation report was published in December 2012. Multidisciplinary cancer care continues to expand to other interventions, such as psychosocial support, genetics and frailty aspects. This is evidenced by the 24 parties that contributed to the development of the last SONCOS report published in 2018, which contains multidisciplinary standards for 25 tumour types [5].

Essence of population-based quality registry

The question whether cancer care can be reorganized in order to keep our healthcare system sustainable, has been subject of investigation for several years. The Quality of Cancer Care working group of the Dutch Cancer Society has addressed this question since April 2007 [6]. For the first time, considerable hospital variation was shown in the treatment and outcomes of colorectal, breast, bladder and lung cancer. One of the most important recommendations was that more reliable data on hospital variation and targets for improvement should be made available and fed back to clinicians in order to reduce variation and improve outcomes. This has led to a growing interest amongst medical professionals to define and understand their own outcomes. In 2009, the Association of Surgeons of the Netherlands (ASN) proceeded to develop the first national outcomes registry in the Netherlands: the Dutch Surgical Colorectal Audit (DSCA) [7].

This nationwide clinical audit aims to evaluate and improve outcomes of surgical care for colorectal cancer patients. Clinical auditing is known to be a powerful tool to initiate and assess quality improvement programmes. Within an audit cycle, collected data are compared with pre-defined quality indicators and continuously fed back to participating centres [8]. Numerous studies with DSCA data have revealed important areas for improvement [9] [10], but have also shown remarkable improvements in processes and outcomes in colorectal cancer surgery [11] [12].

After the successful initiation of the DSCA, the Dutch Institute for Clinical Auditing (DICA) was founded in 2011, aiming to facilitate the initiation of nationwide audits in a uniform format. Today, DICA facilitates 22 nationwide audits covering a wide range of medical conditions, from breast cancer to Parkinson's disease and obesity [13]. Unique features of DICA audits are the leading role of clinicians in defining the data set, the nation-wide coverage, the secured web-based data collection system, and the rapid online feedback of benchmarked data to participating hospitals for improvement initiatives [7].

In the early years of DICA, the main focus was on evaluating and improving the quality of the surgical treatment of cancer patients. Nowadays, some DICA audits have been expanded to non-surgical treatments, such as radiotherapy and medical oncology, in order to provide more insight in the multimodal aspects of cancer care.

OUTLINE OF THESIS

The advancements in precision medicine together with the continuous expansion of multidisciplinary cancer care and the growing group of (long-term) cancer survivors poses some major challenges in assuring quality. This thesis aims to investigate how quality could be assured facing these trends in cancer care.

Part I: Assuring quality in multidisciplinary cancer care

In gastric cancer surgery, surgery still has a central role in potentially curative treatment. Despite surgical advancements, overall survival remains poor with five-year survival rates of 19% in The Netherlands [14]. The high relapse rate has led to the utilization of perioperative chemotherapy for patients with resectable gastric cancer [15]. This multimodal approach is challenging for assessing quality indicators, as different treatment modalities can influence each other. As gastric cancer is associated with high perioperative morbidity rates [16], it is essential to understand to what extent surgically related adverse events influence the multimodal aspects of the treatment process. In Chapter 2, factors associated with the utilization of adjuvant chemotherapy in patients with resectable gastric cancer are described with a special attention to postoperative complications. The study is conducted with data from the Upper GI Cancer Audit (DUCA). The DUCA was one of the first nationwide registries facilitated by DICA and registers all patients with oesophageal or gastric cancer who underwent surgery with the intent of a resection.

Part II: Assuring quality in precision medicine

For a long time, chemotherapy dominated the field of medical oncology. Patient selection, treatment schedules and toxicities were mainly universal for common chemotherapeutic agents [17]. The wide adoption of precision medicine has changed the field of medical oncology dramatically with major benefits for patient outcomes, but also poses new challenges. Random screening is being replaced by screening against specific critical molecular targets. While standard chemotherapeutic agents are mainly associated with immunosuppression and infections, the new targeted and immunotherapies can induce overwhelming inflammation and autoimmunity [18][19]. Nationwide quality registries could be a valuable mechanism to safely and effectively introduce these new drugs in daily practice.

The first registry of DICA aiming to give insight in the quality of precision medicine in cancer care was set-up in July 2013: the Dutch Melanoma Treatment Registry (DMTR).

For many years, the standard of care for patients with metastatic melanoma was the chemotherapeutic agent dacarbazine, resulting in low response rates and a poor survival of less than six months [20]. The introduction of targeted therapies, such as the BRAF inhibitor vemurafenib [21], and immune checkpoint inhibitors, such as the CTLA-4 antibody ipilimumab [18], marked the first treatments that could prolong life for metastatic melanoma patients. The DMTR documents detailed information on all Dutch patients with unresectable or advanced melanoma since the introduction of the new drugs.

The DMTR unites multiple objectives: I) clinical auditing, II) optimizing transparency of melanoma care, III) providing an insight into real-world outcomes on effects and costs and IV) creating a platform for research. The initiation of the DMTR and an overview of the first results are described in Chapter 3.

Prognostic factors in metastatic melanoma

The approval by the European Medicine Agency (EMA) of new melanoma drugs relies on the results of clinical trials. However, clinical trial populations differ in important ways from patients in daily practice. A recent nationwide study of the Danish Metastatic Melanoma Database showed that 55% of melanoma patients in daily practice would not be eligible for participation in phase III immunotherapy trials [22]. Given the high costs and considerable side effect of the new melanoma drugs, it is of utmost importance to be able to determine who is likely to benefit the most.

Moreover, data from the DMTR shows that over 60% of patients receive two or more lines of therapies [23], but the pivotal trials on which the EMA based their conclusion on drug approval have not yet addressed this issue.

The following chapters show the added value of research with data from the DMTR, complementing the information from pivotal trials.

Chapter 4 describes prognostic factors associated with clinical outcomes in BRAF-mutant metastatic melanoma patients treated with vemurafenib in real-world clinical practice. Secondly, it gives an insight in the differences in clinical outcomes across subgroups of patients with different risk profiles.

Although long-term survival may be achieved in a subgroup of patients, there is still an unmet medical need for patients with aggressive disease, in particular for patients with baseline serum LDH of ≥2x upper limit of normal (ULN). Clinicians and researchers worldwide are searching for treatment strategies to improve the very poor prognosis of these patients Chapter 5 investigates whether BRAF inhibitor induction treatment preceding immunotherapy in patients with a baseline serum LDH of ≥2x ULN can be beneficial.

Part III: Assuring quality focusing on patient centred outcomes

With the emerging group of cancer survivors, monitoring functional and QoL outcomes becomes more important, while standardized data on these outcomes are lacking [24]. Doctors typically ask patients about their symptoms only during outpatient visits without collecting this information in a standardized manner.

Secondly, patients today take an active role in their care, from the moment of diagnosis to follow-up. Currently, the information given to support treatment choices is mostly based on clinical outcomes, such as overall survival or disease free survival, whereas many studies showed that the impact on quality of life (QoL) is just as important [25] [26]. This suggests that reliable and valid patient-reported outcomes in addition to clinical outcomes are needed as a basis for constructive treatment discussions between doctors and patients.

Fortunately, there is a growing recognition of the importance of collecting patient-centered outcomes systematically. In 2012, a joint taskforce of the Karolinska Institute in Sweden, the Harvard Busines School and the Boston Consulting group, initiated the International Consortium for Health Outcomes Measurement (ICHOM). The mission of ICHOM is to develop global standard sets of outcomes measures that matter most to patients.

Chapter 6 and chapter 7 describe the process facilitated by ICHOM by which comprehensive standard sets for two of the most common cancer diagnoses (colorectal and breast cancer) were developed. The development process involved a combination of literature review and use of extensive international patient and clinician input.

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Part I

Assuring quality in multidisciplinary cancer care

2 Hospital variation and the impact of postoperative complications on the use of perioperative chemo(radio)therapy in resectable gastric cancer. Results from the Dutch Upper GI Cancer Audit

Schouwenburg MG, Busweiler LAD, Beck N, Henneman D, Amodio S, van Berge Henegouwen MI, Cats A, van Hillegersberg R, van Sandick JW, Wijnhoven BPL, Wouters MWJ, Nieuwenhuijzen GAP; Dutch Upper GI Cancer Audit group

Eur J Surg Oncol 2018 Apr;44(4):532-538

ABSTRACT

Background: Dutch national guidelines on the diagnosis and treatment of gastric cancer recommend the use of perioperative chemotherapy in patients with resectable gastric cancer. However, adjuvant chemotherapy is often not administered. The aim of this study was to evaluate hospital variation on the probability to receive adjuvant chemotherapy and to identify associated factors with special attention to postoperative complications.

Methods: All patients who received neoadjuvant chemotherapy and underwent an elective surgical resection for stage IB-IVa (M0) gastric adenocarcinoma between 2011 and 2015 were identified from a national database (Dutch Upper GI Cancer Audit). A multivariable linear mixed model was used to evaluate case-mix adjusted hospital variation and to identify factors associated with adjuvant therapy. Results: Of all surgically treated gastric cancer patients who received neoadjuvant chemotherapy (n ¼ 882), 68% received adjuvant chemo(radio)therapy. After adjusting for case-mix and random variation, a large hospital variation in the administration rates for adjuvant was observed (OR range 0.31 e7.1). In multivariable analysis, weight loss, a poor health status and failure of neoadjuvant chemo-therapy completion were strongly associated with an increased likelihood of adjuvant therapy omission. Patients with severe postoperative complications had a threefold increased likelihood of adjuvant therapy omission (OR 3.07 95% CI 2.04e4.65).

Conclusion: Despite national guidelines, considerable hospital variation was observed in the probability of receiving adjuvant chemo(radio)therapy. Postoperative complications were strongly associated with adjuvant chemo(radio)therapy omission, underlining the need to further reduce perioperative morbidity in gastric cancer surgery.

INTRODUCTION

Surgery is the cornerstone of curative treatment for patients with gastric cancer. However, optimal surgical treatment provides long-term survival in only 20e30% of the patients [1,2] The high relapse rate has led to the utilization of perioperative treatment modalities, with adjuvant chemoradiotherapy being the preferred treatment in the United States [3] and perioperative chemotherapy in Europe [4,5]. Adjuvant chemotherapy is presumed to be an important component of perioperative chemotherapy, since several Asian studies showed a survival benefit with adjuvant chemotherapy regimens alone [6,7].

Dutch guidelines recommend perioperative chemotherapy containing the ECF (epirubicin, cisplatin and 5-fluorouracil) regimen for patients with resectable gastric cancer who are eligible in terms of physical condition and comorbidity [8]. Despite national guidelines, only half of the patients receive perioperative chemotherapy in Dutch clinical practice [9]. It remains to be elucidated whether this relates to low compliance with national guidelines or to the variation in frailty and comorbidities of the unselected patient population. Previous population-based studies confirmed that both patient and tumour characteristics influence the probability of receiving perioperative treatment, including a higher age, more comorbidity and a lower clinical tumour stage [9-12].

However, it is not well understood to what extent perioperative complications influence the probability of receiving adjuvant chemo(radio)therapy in patients who are considered eligible for multimodal treatment. Gastric surgery is associated with relatively high perioperative complication rates [13], which, by decreasing patient's condition, could have a major influence on the probability of receiving the adjuvant component of perioperative chemo(radio) therapy.

Furthermore, to what extent the use of guideline-recommended adjuvant chemo-(radio)therapy varies between hospitals is not fully elucidated.

The aim of this study was to evaluate hospital, patient, tumour and treatment factors that influence the utilization of the adjuvant component of the perioperative

chemo(radio)therapy regimen for surgically treated gastric cancer patients in the Netherlands.

METHODS

Since 2011, all patients with the intent of a resection for oesophageal or gastric cancer in the Netherlands are registered in the Dutch Upper Gastrointestinal Cancer Audit (DUCA) [14]. The DUCA was set up as a nationwide surgical quality improvement programme. The main objective of the audit is to report risk-adjusted process and outcome information to participating hospitals for internal quality improvement purposes.

Detailed information on patient- and disease-specific characteristics as well as information on the diagnostic process, treatment and perioperative outcome is collected prospectively. Data are compared with an external data registration, the Netherlands Cancer Registry (NCR), on completeness and accuracy. The NCR registers all newly diagnosed malignancies in the Netherlands [2]. The concordance of the DUCA registration with the data set of the NCR on a national level is very high, and has been estimated to be 98% of all gastric cancer resections in 2013 [14].

Patient selection

All patients who were planned to receive the standard perioperative chemo (radio) therapy and received neoadjuvant chemo-therapy and underwent a curative resection for primary gastric cancer between 2011 and 2015 were selected. A curative resection was defined as a curative macroscopically complete resection and no signs of metastatic disease at time of diagnosis and at surgery. Tumour stage was defined according to the seventh edition of the International Union Against Cancer tumour node metastasis (TNM) classification [15]. According to the 7th TNM classification, gastro-oesophageal junction (GEJ) tumours were classified as oesophageal tumours in the DUCA database and were therefore excluded from this study. Patients were considered not eligible for analyses when information was missing regarding the location of the tumour, date of birth, date of surgery, intent of surgery, treatment modalities received and the patient's vital status 30 days post-operatively and/or

at time of discharge. Patients with other treatment regimens, such as neoadjuvant chemo (radio)therapy alone or adjuvant chemo(radio)therapy alone, were excluded.

In order to investigate current hospital variation, hospitals that stopped performing gastric cancer surgery during the study period were excluded.
Patients were classified to the hospital of surgical treatment, since the hospital of diagnosis or the hospital of chemo(radio) therapy is not registered in the DUCA.
For this study, no ethical approval or informed consent was required under Dutch law.

Variables

The studied variables included patient characteristics (age, sex, weight loss before surgery, American Society of Anesthesiologists (ASA) classification, comorbidity according to the Charlson Co-morbidity Index (CCI) [16]), tumour characteristics (tumour site, clinical and pathological tumour stage, differentiation grade) and treatment characteristics (histologic regression after neoadjuvant therapy, radicality of resection, completion of neoadjuvant therapy, intraoperative complications and severe postoperative complications). Hospital stay was defined as days between date of surgery and date of discharge. Postoperative mortality was defined as death within 30 days from the date of surgery or during the initial hospital admission.

A severe postoperative complication was defined as a complication within 30 days with a Clavien-Dindo classification of grade III (requiring surgical, endoscopic or radiological intervention), grade IV (requiring intensive care (IC) management) or grade V (leading to death) [17] Complications were classified into non-surgical complications (e.g. pulmonary, cardiac, thromboembolic, neurologic, urologic complications) or surgical complications (e.g. anastomotic leakage, chylous leakage, haemorrhage, wound and intra-abdominal abscess, pancreatitis).

Treatment groups

Patients were grouped into two treatment categories: receipt of neoadjuvant chemotherapy component alone or receipt of the complete perioperative regimen. Perioperative therapy was defined as neoadjuvant chemotherapy (three cycles of ECF, ECC or EOX) and either adjuvant chemotherapy (three cycles of ECF/ECC or

EOX) or adjuvant chemoradiotherapy with cisplatin and capecitabine according to the CRITICS trial; a large randomized phase III trial evaluating the added value of adjuvant chemoradiotherapy after neoadjuvant chemotherapy that ran during the study period [18].

Statistical analysis

Patient, tumour and treatment characteristics between both treatment groups were compared using the chi-square test for categorical variables and the independent two-sample t-test for continuous variables.

To quantify the true hospital variation for the use of adjuvant chemo(radio)therapy, adjusting for case-mix factors (non-modifiable patient and tumour-specific risk factors that can influence the outcome) was required [19]. Available case-mix factors that can influence the use of adjuvant chemo(radio)therapy were entered in a multivariable linear mixed model: age, sex, weight loss before surgery, ASA classification, CCI, pathologic tumour and nodal stage, tumour location, histologic tumour regression and tumour differentiation. Missing items were included in the analysis as a separate category if exceeding 5%. To account for the hierarchical nature of patients nested within hospitals, the hospital was included as a random effect [19]. The case-mix and random effect adjusted log odds of adjuvant chemo(radio)therapy per hospital were individually presented with the hospital-specific 95% confidence intervals (CIs). The log odds could then be converted into an odds ratio (OR) by taking the exponential. The variation in use of adjuvant chemo(radio)therapy between hospitals was tested for statistical significance with the likelihood ratio test.

Secondly, a univariable and multivariable linear mixed model were used to quantify the association of patient, tumour and treatment factors with the omission of adjuvant chemo(radio) therapy. The multivariable analysis for adjuvant therapy omission was repeated to evaluate the association of surgical and non-surgical complications separately. As a sensitivity analysis, we also assessed the association of severe complications on adjuvant therapy in a younger (<70 years) and healthier (ASA classification I-II, minor weight loss of <5 kg) cohort of patients. Statistical significance was defined as a two-sided p value < .05. All analyses were performed in PASW Statistics version 20 (SPSS inc Chicago, IL, USA) and R version 3.2.2.

RESULTS

Use of perioperative chemo(radio)therapy

Between January 1st, 2011 and December 31st, 2015, 882 patients who received neo-adjuvant chemotherapy and underwent a curative resection for gastric cancer were registered in 24 hospitals (Figure 1). In total, 167 patients (18%) started with the neoadjuvant therapy but did not complete the regimen due to toxicity. Of the remaining, 280 patients only completed the neoadjuvant component (32%) and

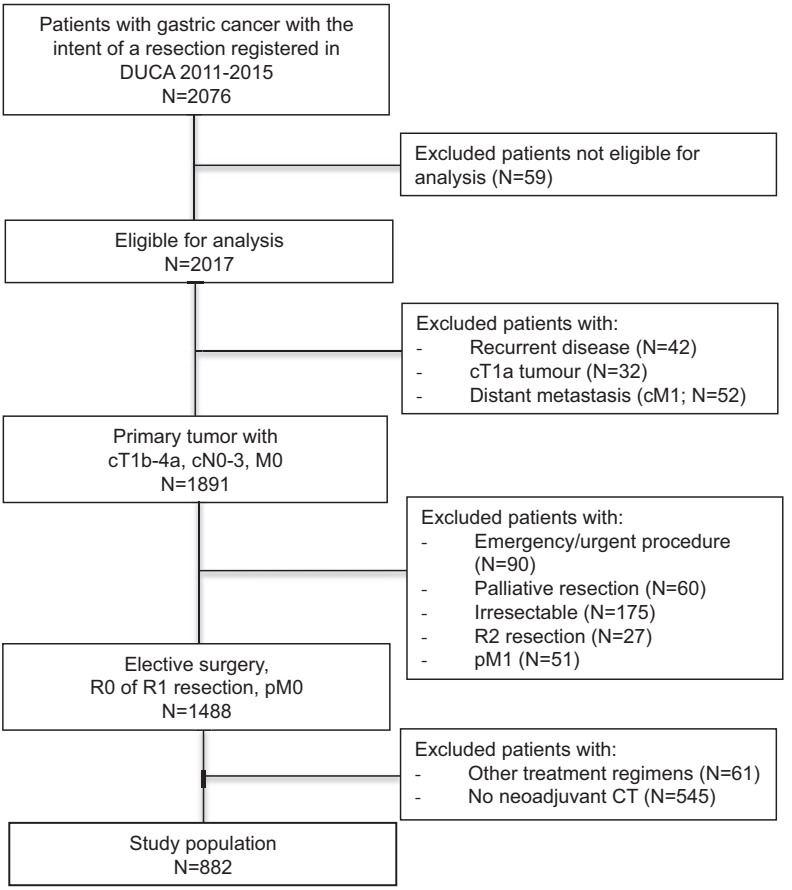

Figure 1. Study population. DUCA = Dutch Upper Gastro-Intestinal Cancer Audit, CT = chemotherapy.

602 patients (68%) received the whole perioperative chemo(radio)therapy regimen (Table 1). Patients with perioperative chemo (radio)therapy were younger, with less weight loss, less comorbidities, completed neoadjuvant chemotherapy more often, had a better tumour response to chemotherapy and experienced postoperative complications less frequently compared to patients with neoadjuvant chemotherapy alone. Sixteen patients (2%) died within the hospitalization or 30 days after surgery, all due to severe postoperative complications.

Table 1. Patient and tumour characteristics.

	Neoadjuvant CT only N=280 N (%)	Perioperative therapy[a] N=602 N (%)	*P*
Age, mean [range], years	67 [31-83]	63 [22-83]	<.001[b]
Age, years			
<60	56 (20)	206 (34)	<.001
60-69	109 (39)	225 (37)	
≥70	115 (41)	171 (28)	
Sex			
Male	175 (63)	395 (66)	.368
Female	105 (38)	207 (34)	
Weight loss			
0kg	62 (22)	172 (29)	.001
1-5kg	51 (18)	154 (26)	
6-10kg	75 (27)	134 (22)	
>10kg	45 (16)	52 (9)	
Unknown	47 (17)	90 (15)	
ASA classification			
ASA I	20 (7)	145 (24)	<.001
ASA II	178 (64)	353 (59)	
ASA III+	79 (28)	103 (17)	
Unknown	3 (1)	1 (0)	
Charlson Comorbidity Index			
Charlson 0	128 (46)	348 (58)	.001
Charlson 1	62 (22)	128 (21)	
Charlson 2+	90 (32)	126 (21)	

Table 1. Patient and tumour characteristics (*continued*)

	Neoadjuvant CT only N=280 N (%)	Perioperative therapy[a] N=602 N (%)	*P*
Clinical tumour stage[c]			
I	41 (15)	99 (16)	.062
II	117 (42)	271 (45)	
III	35 (13)	52 (9)	
Unknown	87 (31)	180 (30)	
Pathological tumour stage[c]			
I	69 (25)	151 (25)	0.003
II	73 (26)	200 (33)	
III	90 (32)	207 (34)	
Unknown	48 (18)	44 (7)	
Site of tumour			.346
Fundus	31 (11)	52 (9)	
Corpus	93 (33)	214 (36)	
Antrum / pylorus	116 (41)	260 (43)	
Whole stomach	19 (7)	40 (7)	
Other	4 (1)	15 (3)	
Unknown	17 (6)	21 (4)	
Histologic regression			
None	88 (31)	146 (24)	<.001
Partial/complete	107 (38)	351 (58)	
Unknown	85 (30)	105 (17)	
Differentiation grade			
Well/moderately	89 (32)	162 (27)	.034
Poorly/Undifferentiated	157 (56)	327 (54)	
Unknown	34 (12)	113 (19)	
Radical resection			
R0	246 (88)	545 (91)	.282
R1	32 (11)	50 (8)	
Unknown	2 (1)	7 (1)	

Table 1. Patient and tumour characteristics (*continued*)

	Neoadjuvant CT only N=280 N (%)	Perioperative therapy[a] N=602 N (%)	*P*
Neoadjuvant therapy completed[d]			
No	111 (40)	56 (9)	<.001
Yes	166 (59)	543 (90)	
Unknown	3 (1)	3 (1)	
Intraoperative complications			
No	263 (94)	581 (97)	.079
Yes	17 (6)	21 (4)	
Postoperative complications[e]			
No	151 (54)	428 (71)	<.001
Yes, grade I-II	24 (9)	62 (10)	
Yes, grade III-V	105 (38)	112 (19)	
Surgical	35 (7)	34 (6)	
Non-surgical	28 (13)	43 (7)	
Surgical and non-surgical	33 (16)	19 (3)	
Unknown	9 (4)	16 (3)	
Postoperative mortality			
No	264 (94)	602 (100)	<.001
Yes	16 (6)	0 (0)	
Hospital stay (median), days	10	8	<.001[b]

ASA=American Society of Anesthesiologists; CT=chemotherapy.

[a]Neoadjuvant chemotherapy combined with adjuvant chemo(radio)therapy

[b]Analysis performed independent two-sample t-test

[c] Tumour Node Metastasis system (7th edition)

[d] More than 80% of cycles were completed

[e] Classified according to Clavien-Dindo classification. Postoperative complications of grade III or higher are considered severe.

Hospital variation in the use of adjuvant chemo(radio)therapy

Unadjusted hospital variation in the administration of adjuvant chemo(radio)therapy ranged from 9% to 94%. A likelihood ratio test showed that the variability between hospitals for use of adjuvant chemo(radio)therapy was statistically significant (p value < .01). After adjustment for case-mix variables and fitting a random effect model, still considerable variation remained (Figure 2). Three hospitals administered

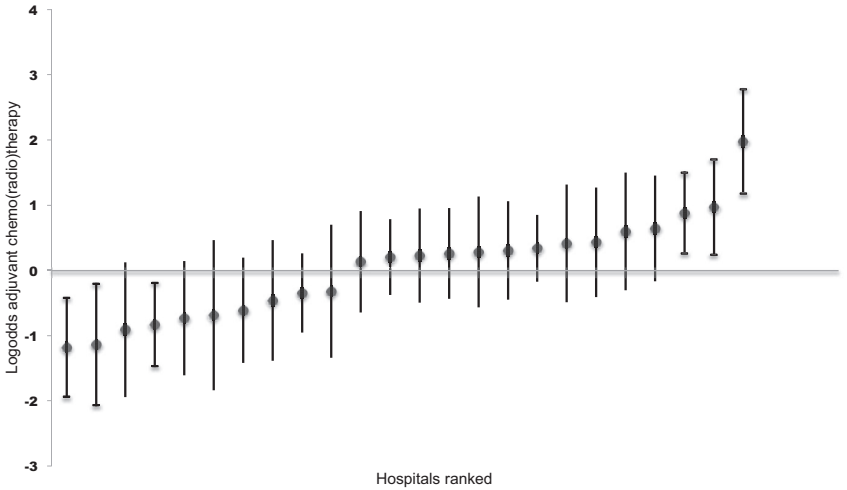

Figure 2. Hospital variation on the administration adjuvant chemo(radio)therapy on the log odds scale. Every hospital is presented as a dot with hospital specific 95% confidence interval, adjusted for case-mix with random-effects models. The zero-line represents the national average. Hospitals with an outcome less than 0 and marked with a dash (-) are negative outliers and have administered significantly less than average. Hospitals with an outcome above 0 and marked with a dash (-) are positive outliers and have administered significantly more than average.

significantly less neoadjuvant chemotherapy (negative outliers) and three hospitals administered significantly more chemotherapy (positive outliers) compared to the national average (range on log odds scale is -1.37-1.36, meaning a range on the odds scale of 0.31-7.2). Hence, in the hospital with the highest administration rate, patients were seven times more likely to receive adjuvant chemo(radio)therapy compared to the national average, irrespective of patient- and tumour-specific risk factors. In the hospital with the lowest administration rate, adjuvant chemo(radio)therapy was three times more likely to be omitted compared to the national average.

Effect of patient, tumour and treatment risk factors on adjuvant chemo(radio)therapy omission

Multivariable analysis showed that women, patients with severe weight loss, a higher ASA classification, failure of neoadjuvant chemotherapy completion and postoperative severe complications were most strongly associated with an increased likelihood of the omission of adjuvant chemo (radio)therapy (Table 2).

Table 2. Univariable and multivariable linear mixed model of patient, tumour and treatment factors associated with the omission of adjuvant chemo(radio)therapy.

Factor	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age				
<60	ref		ref	
60-69	**2.78 (1.23-2.69)**	**<.001**	1.42 (0.87-2.30)	.208
>/= 70	**2.47 (1.70-3.61)**	**<.001**	**1.80 (1.10-3.01)**	**.036**
Sex				
Male	ref		ref	
Female	1.15 (0.85-1.54)	.368	**1.50 (1.02-2.22)**	**.036**
Weight loss				
0kg	ref		ref	
1-5kg	0.92 (0.60-1.41)	.699	1.06 (0.62-1.82)	.967
6-10kg	1.56 (1.04-2.32)	.33	1.57 (0.93-2.65)	.125
>10kg	**2.40 (1.47-3.93)**	**.001**	**2.31 (1.22-4.38)**	**.030**
Unknown	1.45 (0.92-2.29)	.112	1.47 (0.81-2.67)	.338
ASA classification				
ASA I	ref		ref	
ASA II	**3.66 (2.22-6.03)**	**<.001**	**2.04 (1.12-3.72)**	**.021**
ASA III+	**5.56 (3.20-9.66)**	**<.001**	**2.82 (1.41-5.66)**	**.005**
Charlson score				
Charlson 0	ref		ref	
Charlson 1	1.31 (0.91-1.90)	.139	1.01 (0.63-1.61)	.838
Charlson 2+	**1.94 (1.39-2.72)**	**<.001**	1.39 (0.88-2.19)	.101
Pathological tumour stage[a]				
I	ref		ref	
II	0.80 (0.54-1.18)	.260	**0.53 (0.32-0.87)**	**.012**
III	0.95 (0.65-1.39)	.796	**0.48 (0.28-0.83)**	**.008**
Unknown	**2.39 (1.45-3.93)**	**.001**	0.70 (0.34-1.43)	.322
Site of tumour				
Corpus	ref		ref	
Fundus	1.37 (0.83-2.28)	.222	1.73 (0.89-3.35)	.115
Antrum/pylorus	1.02 (0.74-1.42)	.875	0.90 (0.58-1.38)	.898
Whole stomach	1.09 (0.601-1.99)	.771	1.21 (0.54-2.71)	.545
Unknown	1.34 (0.74-2.42)	.329	1.23 (0.56-2.67)	.661

Table 2. Univariable and multivariable linear mixed model of patient, tumour and treatment factors associated with the omission of adjuvant chemo(radio)therapy (*continued*)

Factor	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Differentiation				
Good/medium	ref		ref	
Bad/none	1.14 (0.83-1.58)	.411	0.92 (0.60-1.42)	.980
Unknown	**0.63 (0.41-0.96)**	**.032**	0.69 (0.38-1.27)	.367
Histologic regression				
Partial/complete	ref		ref	
None	**1.98 (1.41-2.78)**	**<.001**	**1.68 (1.05-2.69)**	**.023**
Unknown	**2.66 (1.96-3.8)**	**<.001**	**2.13 (1.26-3.58)**	**.003**
Radical resection				
R0	ref		ref	
R1	1.42 (0.89-2.27)	1.44	1.36 (0.70-2.66)	.481
Neoadjuvant therapy completed[b]				
Yes	ref		ref	
No	**6.48 (4.5-9.34)**	**<.001**	**6.55 (4.14-10.35)**	**<.001**
Intraoperative complications				
No	ref		ref	
Yes	1.79 (0.93-3.45)	.082	1.82 (0.77-4.30)	.179
Severe postoperative complications				
No	ref		ref	
Grade I-II	1.1 (0.67-1.82)	.72	1.36 (0.73-2.53)	.439
Grade >III	**2.66 (1.92-3.68)**	**<.001**	**3.07 (2.04-4.65)**	**<.001**

Bold printed numbers are statistically significant ($p<0.05$).

ASA=American Society of Anesthesiologists, CI=confidence interval.

[e] Tumour Node Metastasis system (7th edition)

[b] More than 80% of cycles were completed

Severe postoperative complications increased the likelihood of adjuvant treatment omission more than threefold (OR 3.07; 95% CI2.04-4.65). Additional multivariable analysis showed that severe surgical complications displayed a greater effect on the probability of the omission of adjuvant chemo(radio)therapy than severe non-surgical complications (OR 3.42 95% CI 1.93-6.04 vs 1.85 95% CI 1.02-3.37). Patients with a combination of both severe surgical and severe non-surgical complications had

the highest likelihood of adjuvant chemo(radio)therapy omission (OR5.54 95%CI 2.77- 11.07).
After further selecting a younger cohort of patients with less comorbidities and weight loss (<70 years, ASA I-II, weight loss <5 kg; N = 267), 81% received adjuvant chemotherapy and 20% experienced a severe postoperative complication. After adjustment, an increase in the likelihood of adjuvant treatment omission following severe postoperative complications was also found in this subgroup (OR 2.45 95% CI 1.15-5.25).

DISCUSSION

This population-based study shows that after completing the neoadjuvant therapy, only 68% of surgically treated gastric cancer patients receive the adjuvant chemo(radio)therapy component of the perioperative chemo(radio)therapy regimen. Furthermore, a significant hospital variation is observed in the probability of receiving adjuvant treatment, with postoperative severe surgical complications having a major impact.

Similar compliance rates of adjuvant chemo(radio)therapy were observed in this study as those shown in the MAGIC trial (68% vs 65%, respectively) [4]. The ACTS-GC and CLASSIC trial evaluated the effect on survival of adjuvant chemotherapy alone and reported comparable compliance rates of 67% [6,7]. This indicates the difficulty of delivering the adjuvant component following gastric surgery, even in selected patient populations. Apparently, the treating physicians and/or patients are reluctant to administer the adjuvant component in older and frail patients because of perceived toxicity of the regimen in the trials and uncertainty on long-term harms and benefits. These results show the need for specific guidelines that are more tailored to individual patients and subgroups.

Considerable hospital variation was observed with regard to the use of adjuvant chemo(radio)therapy, even after adjustment for case-mix factors and random variation. In hospitals with the lowest administration rates, adjuvant chemo(radio) therapy was three times more likely to be omitted compared to the national average,

suggesting that underuse of adjuvant chemotherapy is not merely a reflection of the age or comorbidity burden, but it may also reflect other (hospital specific) factors. Previous studies demonstrated that consultation of a medical oncologist [10] and a dedicated multi-disciplinary team meeting [11] are independently associated with higher rates of adjuvant chemo(radio)therapy receipt, which underlines the importance of the decisional process.

The effect of hospital variation in adjuvant chemotherapy use on overall survival has not been studied yet. A recent Dutch study on gastric cancer patients demonstrated significant hospital variation in the probability to receive potential curative surgical treatment [20]. Patients diagnosed in hospitals with a lower probability of undergoing surgical treatment had a worse overall survival [20]. Future studies are needed to explore whether a lower hospital probability of chemotherapy use is also associated with poorer survival.

A very strong effect of severe postoperative complications on the probability to omit adjuvant chemo(radio)therapy was demonstrated, which increased more than threefold compared to patients who had no complications. This has also been reported for other oncologic procedures with high perioperative morbidity rates, including procedures for colorectal and pancreatic cancer [21e24]. A recent retrospective multicentre US study in resectable gastric cancer patients showed that the combination of experiencing postoperative complications and not subsequently receiving adjuvant chemo(radio)therapy increased the long-term overall mortality twofold [25].

Optimal treatment comprises not merely the administration, but also a timely start after surgery and completion of all planned cycles of chemotherapy. Two recent Asian studies on timing of adjuvant chemotherapy in resectable gastric cancer showed that delayed treatment after 8 weeks was associated with worse survival outcomes [26,27]. They also demonstrated that the occurrence of postoperative surgical complications was the strongest factor related to this delay. Like our study, this indicates that complications following gastric cancer surgery not only affect short-term outcomes, but also influence long-term survival. This phenomenon might be related to the omission or delay of adjuvant treatment.

Gastric cancer surgery is complex and has a relatively high incidence of postoperative complications. This study showed that the effect of surgical complications on the omission of adjuvant chemotherapy is much stronger than that of non-surgical complications (OR 3.4 vs 1.9, respectively). Even among the healthier and younger patient cohort, severe complications were common (20%) with an over twofold increased likelihood of adjuvant chemo(-radio)therapy omission. Many efforts aimed to improve the outcome of gastric cancer surgery have been made, such as the centralization and the initiation of clinical audits [28]. Despite these efforts, severe complication rates remain high, ranging from 20% to 35% in Western countries [13,29].

This study has several strengths and limitations. The strength of this study is the population-based and prospective nature of the audit, including all Dutch hospitals with a 98% national coverage of all gastric cancer resections. It therefore reflects daily practice and is highly representative of the Dutch population. However, the DUCA has its focus on the quality of surgical treatment and short-term outcomes of care. Therefore, detailed information on the chemotherapy regimen, the number of received cycles, dosage, toxicity, reasons for not receiving chemotherapy and long-term follow-up is not registered. A multidisciplinary extension of the audit, including participation of medical oncologists, pathologists, gastroenterologists and radiation oncologists and merging DUCA data with survival data of the National Cancer Registry may offer a better understanding of the decision-making process and treatment patterns for multimodal therapy and ultimately the impact on long-term survival.

Furthermore, the DUCA does not register the hospital of diagnosis, and actual referral patterns could therefore not be revealed. Since centralization of surgical treatment of gastric cancer in the Netherlands has been introduced in 2013 with a minimum requirement of 20 resections per hospital annually, an increasing number of patients are referred for surgery from another hospital. However, perioperative treatment is not centralized and the hospital variation as shown in this study might thus also be related to the variation in decision-making on (neo)adjuvant treatment in hospitals of diagnosis.

These findings broaden our understanding of decision-making in the use of adjuvant chemotherapy for gastric cancer in daily clinical practice. In addition to the well-known patient and tumour factors associated with its use, the occurrence of post-operative surgical complications also has a major effect on adjuvant chemo(radio) therapy omission and might eventually affect long-term survival. Further efforts should therefore be made to decrease the incidence of complications and to improve recognition and management of perioperative morbidity to reduce omission of adjuvant treatment.

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Part II

Assuring quality in precision medicine

3 Dutch Melanoma Treatment Registry: quality assurance in the care of patients with metastatic melanoma in the Netherlands

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Eur J Cancer 2017 Feb;72:156-165

ABSTRACT

Background: In recent years, the treatment of metastatic melanoma has changed dramatically due to the development of immune checkpoint and mitogen-activated protein (MAP) kinase inhibitors. A population-based registry, the Dutch Melanoma Treatment Registry (DMTR), was set up in July 2013 to assure the safety and quality of melanoma care in the Netherlands. This article describes the design and objectives of the DMTR and presents some results of the first 2 years of registration.

Methods: The DMTR documents detailed information on all Dutch patients with unresectable stage IIIc or IV melanoma. This includes tumour and patient characteristics, treatment patterns, clinical outcomes, quality of life, healthcare utilisation, informal care and productivity losses. These data are used for clinical auditing, increasing the transparency of melanoma care, providing insights into real-world cost-effectiveness and creating a platform for research. Results: Within 1 year, all melanoma centres were participating in the DMTR. The quality performance indicators demonstrated that the BRAF inhibitors and ipilimumab have been safely introduced in the Netherlands with toxicity rates that were consistent with the phase trials conducted. The median overall survival of patients treated with systemic therapy was 10.1 months (95% confidence interval [CI] 9.1e11.1) in the first registration year and 12.7 months (95% CI 11.6e13.7) in the second year.

Conclusion: The DMTR is the first comprehensive multipurpose nationwide registry and its collaboration with all stakeholders involved in melanoma care reflects an integrative view of cancer management. In future, the DMTR will provide insights into challenging questions regarding the definition of possible subsets of patients who benefit most from the new drugs.

INTRODUCTION

Malignant melanoma is one of the most aggressive types of skin cancer. The incidence of melanoma has increased in Europe over the past few decades [1,2]. In the Netherlands, the number of new cases of invasive melanoma (all stages) more than doubled between 2000 and 2014 and it accounts for approximately 90% of skin-cancer-related mortality in 2014 [3]. The increased incidence accompanied by the high mortality rates made it one of the worst performing tumours in the Netherlands over recent years, especially for males [4].

The treatment of unresectable and metastatic melanoma has changed dramatically in recent years due to the development of immune checkpoint inhibitors (e.g. ipilimumab, nivolumab and pembrolizumab) and inhibitors of the mitogen-activated protein (MAP) kinase pathway (e.g. the BRAF inhibitors vemurafenib and dabrafenib and the MAP kinase (MEK) inhibitors trametinib and cobimetinib) [5-8]. These drugs create new opportunities to prolong progression-free and overall survival (OS) for patients with metastatic melanoma. However, the introduction of the new drugs poses several challenges. First, adequate selection of subsets of patients who may benefit from immune checkpoint inhibitors or MAP kinase inhibitors and sequencing these new drugs present a challenge. Second, experience in recognising and treating the potentially life-threatening side effects of immune checkpoint inhibitors is essential. Finally, the high costs of these new drugs raise questions about their cost-effectiveness in daily clinical practice.

The introduction of the new drugs to treat metastatic melanoma was approved by the Dutch Minister of Health subject to two firm conditions: I) the concentration of metastatic melanoma treatment in a limited number of designated centres and II) the recording of all patients with unresectable or metastatic melanoma (stage IIIc or stage IV melanoma) in a nationwide registry.

To achieve centralisation, the Dutch Society of Medical Oncologists (NVMO) selected 14 hospitals as melanoma centres in 2012. These centres were chosen on the basis of their expertise in the systemic treatment of melanoma, their infrastructure and their geographic distribution. At the same time, a set of multidisciplinary quality standards was established by the professional organisations involved in melanoma treatment, including a minimum volume standard of 20 new patients annually

receiving systemic treatment for meta-static melanoma [9]. This number of patients is based on safety reports in clinical trials [5,6]. In addition, it was assumed that this would allow the centres to have sufficient experience in treating patients with severe toxicity.
The Dutch Melanoma Treatment Registry (DMTR) was set up in July 2013. A unique consortium of organisations, including medical specialists, policymakers, healthcare researchers, patient advocates and pharmaceutical companies, was involved in establishing the registry.
This article describes the design and the objectives of the DMTR and presents some results of the first 2 years of registration.

MATERIALS AND METHODS

Objectives of the DMTR

The DMTR was designed to serve multiple objectives: I) clinical auditing, II) improving transparency concerning the quality of melanoma care, III) providing an insight into real-world outcomes on effects and costs and IV) to create a platform for research.

Clinical auditing: improving melanoma care
Clinical auditing has been recognised as an important tool for quality assessment and improvement [10,11]. The DMTR is used to provide melanoma treatment centres with benchmarked feedback on the number of patients treated, treatment patterns, toxicity rates and survival data on a weekly basis in relation to the national average and in relation to the results of other anonymised melanoma centres. All results are discussed at the quarterly meetings of the Medical Committee in which all centres participate to increase awareness of the quality of care delivered and to stimulate quality improvement initiatives.

Improving transparency of melanoma care: a set of quality standards
Healthcare professionals increasingly need to provide evidence of the quality of the care they deliver [12,13]. A set of well-defined, uniformly collected quality indicators evaluating melanoma care can be derived from data in the DMTR. These quality

indicators are established by the joint efforts of clinical professionals, patient advocates and the National Health Care Institute. These quality indicators at the level of melanoma centre will gradually be made publicly available to all stakeholders involved in melanoma care.

Real-world outcomes: cost-effectiveness of the new drugs
It is of great importance to assess the quality of life and cost-effectiveness of the new drugs in clinical practice. The DMTR, therefore, not only collects clinical data, but also data on quality of life, healthcare utilisation, informal care and productivity losses. These data will be used to develop a health economic disease model to evaluate the real-world cost-effectiveness of treatment for metastatic melanoma.

Platform for research
A population-based registry is a valuable resource for research as it provides real-world data, including information on patients often not eligible for clinical trials. Exploratory comparative effectiveness studies may be conducted with DMTR data if randomised controlled trials are not yet available.

Main structures of the DMTR

Funding
The initial costs of developing the DMTR database were funded through a grant from the Netherlands Organisation for Health Research and Development (ZonMw). The pharmaceutical companies (Roche Nederland B.V., Bristol-Myers Squibb, and GlaxoSmithKline/Novartis, participating from the establishment of the registry, and MSD, participating since 1 July 2015), which produce the newly approved drugs, funded the first 4 years of registration. Future funding will be created in collaboration with the pharmaceutical companies, health insurance companies and melanoma centres.

Organisational structure
The DMTR is a collaboration of multiple stakeholders involved in the treatment of metastatic melanoma. The NVMO is the official representative of all medical oncologists in the Netherlands. The NVMO is the initiator of the DMTR and together with the patient advocacy

(Stichting Melanoom) and the Working Group on Immunotherapy and Oncology (WIN-O), they form the Board of Directors.
The Dutch Institute for Clinical Auditing (DICA) facilitates the implementation of the DMTR and supervises data collection and management. The DICA is specialised in the uniform collection of data and in making appropriate adjustments to case-mix variations between hospitals to provide benchmarked feedback. The methods for case-mix adjustment are described in more detail elsewhere [14].
The Institute for Medical Technology Assessment (iMTA) cooperates with DICA and is responsible for reporting on the cost-effectiveness of the new drugs for advanced melanoma. The iMTA is a scientific institute for research in health economics [15].
Trained data managers at the Netherlands Comprehensive Cancer Organisation (IKNL) coordinate and perform data collection in the melanoma centres. IKNL is responsible for the Dutch Cancer Registry, which collects data concerning incidence, prevalence, survival and mortality of all malignancies in the Netherlands [16].

A diagram of the DMTR's organisational structure can be found in Figure 1.

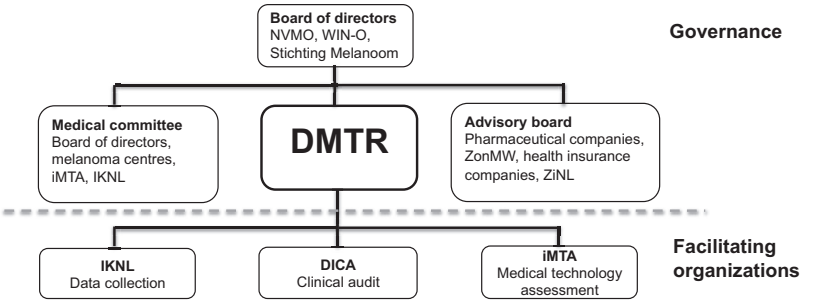

Figure 1. Organisational structure of the Dutch Melanoma Treatment Registry (DMTR). NVMO, Dutch Society of Medical Oncologists; WIN-O, the Working Group on Immunotherapy and Oncology; Stichting Melanoom, patient association; iMTA, Institute for Medical Technology Assessment; ZonMW, Netherlands Organisation for Health Research and Development; ZiNL, National Health Care Institute; DICA, Dutch Institute for Clinical Auditing and IKNL, the Netherlands Comprehensive Cancer Organisation.

Data collection

Dataset

Data collection started in September 2013, retrospectively registering data from patients with metastatic melanoma newly diagnosed (metastatic at first diagnosis) and metastatic upon progression or recurrence who were treated with ipilimumab and/or a BRAF inhibitor from July 2012 to June 2013. During this period, patients not receiving treatment with one of these drugs were not yet registered in the DMTR. From July 2013, all patients diagnosed with metastatic melanoma were prospectively registered irrespective of treatment modality.

An extensive entry in the register was performed for all patients who were referred to a melanoma centre. A concise entry in the register was carried out for patients for whom a melanoma centre was only consulted.

For all extensively monitored patients, the DMTR contains detailed clinical information on patient and tumour characteristics, diagnostics, treatment strategies, adverse events, time to progression and survival. In addition, data are collected on healthcare resource utilisation, informal care, productivity losses and patient-reported outcome measures (PROMs) (i.e. melanoma-specific and overall quality of life).

No ethical approval or informed consent was required under Dutch law to register this information. The clinical dataset is presented as a diagram in Appendix 1.

Web-based environment: data collection, processing and benchmarked feedback

The DMTR uses a web-based environment for data collection and data management including continuous benchmarked feedback to the participating healthcare professionals through a secure website. Pharmaceutical companies are provided with aggregated information regarding the use and performance of their drugs in clinical practice.

Internal and external data verification

Data quality is verified at several key time points along the registration process. Missing or potentially incorrect data are fed back directly to the data managers within the web-based environment. Furthermore, the IKNL data managers verify 10% of the registered data annually. Oncologists supervise the registration process and check all results at patient level. The administrative burden for participating physicians is roughly 30 min per patient record.

Statistical analysis

Descriptive statistics were used to assess patient, tumour and treatment characteristics. The OS was defined as the time from date of diagnosis of metastatic melanoma to death from any cause. Patients alive at time of analysis were censored. The OS with corresponding two-sided 95% confidence interval [CI] was analysed using the Kaplan Meier method. Follow-up time was calculated from first visit to a melanoma centre using the inverse Kaplan Meier method [17]. Performance on the quality indicators is presented in funnel plots using 99% confidence limits that vary in relation to the volume of patients per hospital [18]. All statistical analyses were performed in PASW Statistics version 20 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

From 1st July 2012 to 1st July 2014, 1472 patients with metastatic melanoma were registered in the DMTR. A total of 60 patients were not referred to a melanoma centre and therefore received only a concise entry mainly due to poor performance status or limited prognosis. Of all the patients referred to a melanoma centre (n =1412), 23 patients (1.6%) were excluded because of missing data on date of birth, date of first visit to a melanoma centre, date of diagnosis of disseminated disease and the type of treatment. These items of in-formation were considered to be the minimal requirements for analysis. Complete data was available for 1389 patients. Median follow-up was 18.8 months (95% CI 18.0-19.5) (data cut-off 14th September, 2015).

Baseline patient and tumour characteristics at the first visit to a melanoma centre are shown in Table 1 per registration year. Most patients had a World Health Organization performance score of 0e1 (83% first year and 77% second year), the median age was 59 and 62 years and over half of the patients were male (59% and 54%). Most of the patients had stage M1c disease (78% and 69%) and over a quarter had elevated serum lactate dehydrogenase (LDH) levels (35% and 26%). Furthermore, 23% of patients had brain metastases on radiographic imaging, with more than 10% of these patients having symptomatic brain metastases at first visit.

Table 1. Patient, tumour and treatment characteristics at first presentation in a melanoma centre

Characteristic	July 2012-July 2013 *N*=401 *N* (%)	July 2013- July 2014 *N*=988 *N* (%)
Patient characteristics		
Age, median (range), yrs	59 (20-90)	63 (18-92)
Age group		
< 50	108 (27)	191 (19)
50-59	97 (24)	210 (21)
60-69	118 (29)	291 (30)
=>70	78 (20)	296 (30)
Gender		
Female	163 (41)	453 (46)
Male	238 (59)	535 (54)
Median (range) time since primary diagnosis, yrs	2 (0-28)	2 (0-43)
ECOG performance score		
0	199 (50)	475 (48)
1	132 (33)	251 (25)
>/=2	44 (11)	102 (10)
Unknown	26 (7)	160 (16)
Elevated serum LDH level (>250 U/L)		
No	250 (62)	619 (63)
Yes	139 (35)	252 (26)
Unknown	12 (3)	117 (12)
Brain metastases		
No	290 (72)	664 (67)
Yes	92 (23)	224 (23)
Symptomatic brain metastasis	48 (12)	155 (16)
Unknown	19 (5)	100 (10)
Tumour characteristics		
Disease stage		
Unresectable stage IIIc	8 (2)	55 (6)
M1a	30 (8)	58 (6)
M1b	35 (9)	88 (9)

Table 1. Patient, tumour and treatment characteristics at first presentation in a melanoma centre (*continued*)

Characteristic	July 2012-July 2013 *N*=401 *N* (%)	July 2013- July 2014 *N*=988 *N* (%)
M1c	314 (78)	679 (69)
Unknown M stage	12 (3)	85 (9)
Unknown	2 (1)	23 (2)
Location of primary tumour		
Trunk	169 (42)	330 (33)
Extremities	106 (26)	292 (30)
Head and/or neck	50 (13)	119 (12)
Uveal	5 (1)	69 (7)
Acral	10 (3)	28 (3)
Mucosal	5 (1)	22 (2)
Primary unknown	50 (13)	121 (12)
Missing	6 (2)	7 (1)
Histology of primary tumour[a]		
Superficial spreading	171 (51)	374 (49)
Nodular	86 (26)	207 (27)
Acral lentiginous	5 (2)	16 (2)
Desmoplastic	4 (1)	5 (1)
Lentigo maligna	4 (1)	12 (2)
Other	19 (6)	55 (7)
Unknown	46 (14)	100 (13)
Mutation status		
No mutation status analysed	6 (2)	107 (11)
Mutation status analysed	395 (99)	879 (89)
Unknown	0 (0)	2 (0)
Type of mutation		
BRAF mutation	306 (76)	475 (48)
No BRAF mutation	89 (22)	404 (41)
NRAS mutation[b]	17	146
KIT mutation[b]	2	7
GNAQ mutation[b]	0	7

Table 1. Patient, tumour and treatment characteristics at first presentation in a melanoma centre (*continued*)

Characteristic	July 2012-July 2013 *N*=401 *N* (%)	July 2013- July 2014 *N*=988 *N* (%)
GN-11 mutation[b]	0	1
Wild type[b]	58	209
Type of mutation unknown[b]	12	34
Treatment characteristics		
Previous systemic treatment for metastatic disease		
Chemotherapy	78 (20)	41 (4)
BRAF inhibitor	13 (3)	13 (1)
Ipilimumab	0 (0)	2 (0)
Trial	26 (6)	30 (3)
Treatment in melanoma centre		
Systemic treatment	401 (100)	717 (73)
Only local treatment	N/A	151 (15)
RFA	N/A	2 (0)
Surgery	N/A	60 (6)
Radiotherapy	N/A	68 (7)
Surgery and radiotherapy	N/A	19 (2)
Other	N/A	2 (0)
No therapy	N/A	120 (12)

Yrs=years; ECOG = Eastern Cooperative Oncology Group; LDH= lactate dehydrogenase; RFA = radiofrequency ablation; N/A = not applicable.

[a] Histology is presented for patients with cutaneous melanoma (first registration year, *N*=335; second registration year, *N*=769).

[b] Type of mutation is presented for patients with BRAF, wild-type (first registration year, *N*=89; second registration year, *N*=404).

Treatment characteristics

Figure 2 demonstrates the type of drug administered to patients by line of treatment and by year of registration in the DMTR. In the first registration year, a BRAF inhibitor was most frequently administered in the first line of therapy (66%). Ipilimumab was mostly administered as second-line therapy (39%), but a shift towards first-line

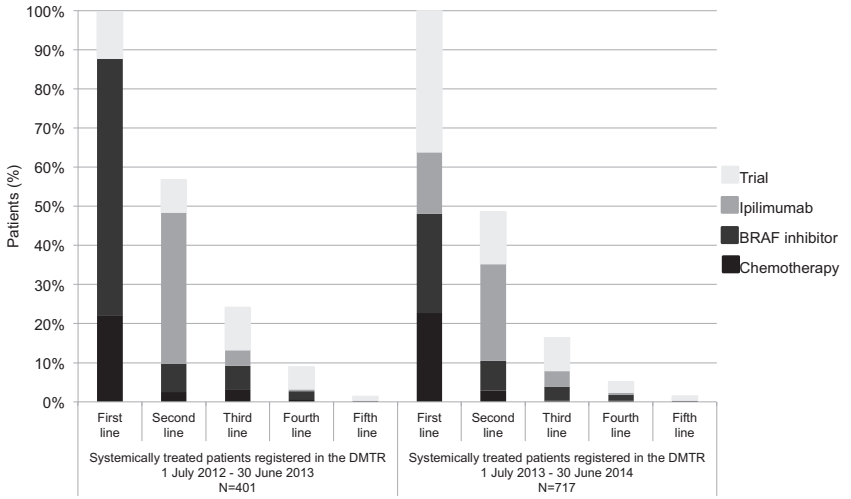

Figure 2. Treatment patterns of all systemically treated patients with metastatic melanoma, presented by line of systemic therapy and year of registration.

therapy (16%) was observed in the second registration year. This was probably due to the approval of ipilimumab as a first-line therapy at the beginning of 2014. More than one-third of the patients (36%) participated in a clinical trial or compassionate-use programme as first-line therapy in the second year.

Performance indicators of quality of metastatic melanoma care

Table 2 shows the indicators for quality of care in the first 2 registration years at national level.

Structure

Participation in the DMTR is obligatory for all 14 melanoma treatment centres and the full participation of all centres was achieved within the first registration year. Of all patients referred to a melanoma centre, 98-100% had sufficient quality of data to include for further analysis.

Outcome

Of all the patients treated with a BRAF inhibitor, almost 30% experienced at least one grade 3 or 4 adverse event. The grade 3/4 adverse events for patients treated with

Table 2. Results of the performance indicators on the quality of metastatic melanoma care

Indicator	2013			2014		
	Eligible patients (*N*)	Observed patients (*n*)	%	Eligible patients (*N*)	Observed patients (*n*)	%
Structure						
Hospitals participating in the Dutch Melanoma Treatment Registry	14[a]	14[a]	100	14[a]	14[a]	100
Patients referred to a melanoma center and eligible for analysis	401	401	100	1011	988	98
Process						
Patients without therapy	-	-		988	120	12
Patients with local therapy	-	-		988	151	15
Patients with systemic therapy	401	401	100	988	717	73
Patients with systemic therapy: chemotherapy[b]	401	34	8	988	156	16
Patients with systemic therapy: a BRAF inhibitor[b]	401	288	72	988	237	24
Patients with systemic therapy: ipilimumab[b]	401	174	43	988	320	32
Short term outcomes						
Patients with grade III-IV AE as a result of treatment with chemotherapy[b]	34	4	12	156	6	4
Patients with grade III-IV AE as a result of treatment with BRAF inhibitor[b]	288	89	31	237	67	28
Patients with grade III-IV AE as a result of treatment with ipilimumab[b]	174	34	20	320	75	23
Deaths associated with grade III-IV AE after treatment with chemotherapy[b]	34	0	0	156	0	0
Deaths associated with grade III-IV AE after treatment with BRAF inhibitor[b]	288	0	0	237	0	0
Deaths associated with grade III-IV AE after treatment with ipilimumab[b]	174	1	1	320	0	0

Table 2. Results of the performance indicators on the quality of metastatic melanoma care (*continued*)

Indicator	2013			2014		
Long term outcomes	Patients at risk (*N*)	Events[c] (*n*)		Patients at risk (*N*)	Events[c] (*n*)	
Overall survival and mortality rates of patients without therapy						
Median OS, months (95% CI)	-	-		120	77	4.5 (1.2-7.9)
6 months, % (95% CI)	-	-		47	62	45 (36-54)
12 months, % (95% CI)	-	-		31	73	34 (25-43)
18 months, % (95% CI)	-	-		17	77	29 (20-38)
Overall survival and mortality rates of patients with local therapy						
Median OS, months (95% CI)	-	-		151	87	10.3 (7.4-13.2)
6 months, % (95% CI)	-	-		83	58	60 (52-68)
12 months, % (95% CI)	-	-		46	78	44 (35-52)
18 months, % (95% CI)	-	-		NR	NR	NR
Overall survival and mortality rates of patients with systemic therapy						
Median OS, months (95% CI)	401	323	10.1 (9.1-11.1)	713	419	12.7 (11.6-13.7)
6 months, % (95% CI)	294	105	73 (68-77)	537	157	78 (75-81)
12 months, % (95% CI)	169	229	43 (38-48)	312	315	53 (49-57)
18 months, % (95% CI)	106	288	28 (23-32)	109	395	37 (32-41)

AE= adverse event, NR=not reached, OS = overall survival

[a] The number displayed corresponds to the number of hospitals

[b] Patients can be treated with more than one type of systemic therapy during the study period

[C] Event: number of deaths

ipilimumab were 20% and 23% in year 1 and 2, respectively. No deaths were related to the toxicity of treatment with a BRAF inhibitor. One death was associated with ipilimumab toxicity. The median OS of patients treated with systemic therapy was 10.1 months (95% CI 9.1- 11.1) in the first year and 12.7 months (95% CI 11.6- 13.7) in the second year. Figure 3 shows the hospital variation in percentage of patients with grade 3/4 adverse events during treatment with a BRAF inhibitor (3a) and ipilimumab (3b) in the first 2 years of registration. The funnel plots demonstrate that no melanoma centre performed significantly worse than average on toxicity rates for both ipilimumab and BRAF inhibitors. One melanoma centre performed significantly better than average on toxicity rates after treatment with a BRAF inhibitor.

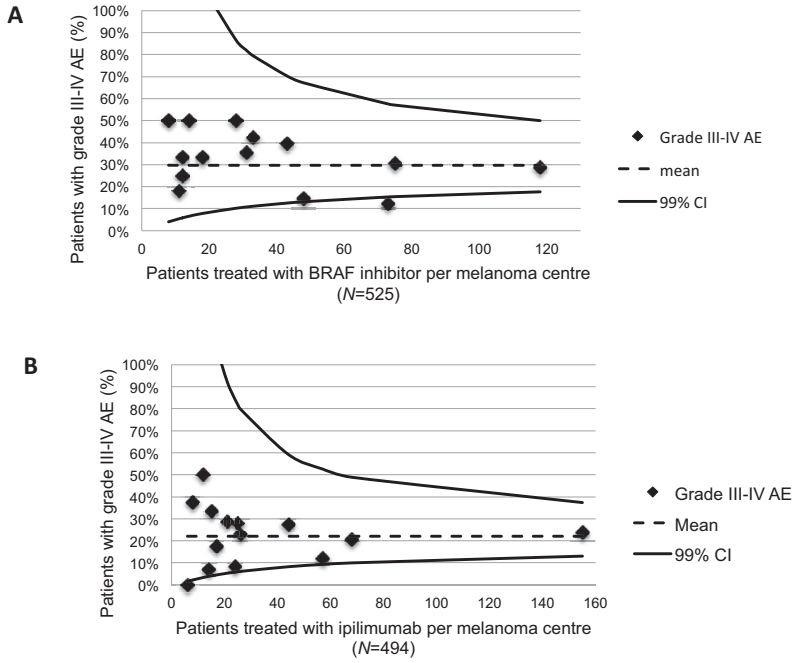

Figure 3. Variation between melanoma centres in the percentage of patients with grade III-IV AEs caused by a BRAF inhibitor (A) and/or ipilimumab (B). The dotted line presents the average percentage of patients who experienced grade III-IV AEs. AE = adverse event.

DISCUSSION

This article reports on the start-up and key elements of the DMTR. The DMTR is unique in its collaboration between all stakeholders involved in treating metastatic melanoma, and its multipurpose design. The active participation of the 14 dedicated melanoma centres led to the nationwide coverage of all patients with meta-static melanoma in the registry within the first year.

The results of the DMTR demonstrate that treatment with BRAF inhibitors and ipilimumab has been implemented as standard of care in the Netherlands. Monitoring these drugs in population-based registries is therefore highly relevant to the assessment of the extent to which results from clinical trials are achieved in clinical practice [19].

The first Dutch population-based registry in outcome research for cancer patients was PHAROS. This haematological registry started in 2010 and was created to serve multiple purposes, including evaluating the quality of care of three haematologic malignancies in daily practice and determining the clinical and cost-effectiveness of treatments used [20].

However, population-based registries are scarce in the field of metastatic melanoma. Existing registries generally have a retrospective design and do not have a nationwide coverage [21]. More importantly, these registries do not include information on patients treated with the new drugs; the reported results are, therefore, not applicable to current management of advanced melanoma [22].

Data from the DMTR demonstrates that BRAF inhibitors and ipilimumab have been safely introduced in the Netherlands. The toxicity rates were comparable with the results in clinical trials [5-8], although a relatively great number of patients registered in the DMTR have brain metastases and/or a poor performance status. These patients would have been ineligible for trial inclusion. Only one death was reported, due to an adverse event contributed to ipilimumab. This may indicate that adequate management of adverse events in specialised melanoma centres with experience in the treatment of patients with advanced melanoma can prevent life-threatening situations in daily practice. BRAF inhibitors and ipilimumab show a survival benefit compared with classic cytotoxic treatment [23,24]. In this study, the 12-month survival rate already improved during the second year of registration. This could be the effect

of the approval of ipilimumab as a first-line therapy and a large number of patients participating in clinical trials with an anti-PD1 antibody. With the rapid development of new drugs and the combination of drugs [25,26], we expect the survival of metastatic melanoma patients to improve.

Real-time feedback and transparency are essential to evaluating and anticipating the rapid advances in met-astatic melanoma treatment, but existing quality initiatives concerning melanoma care have mainly focused on surgical treatment [11,27]. The DMTR provides clinicians with benchmarked feedback with detailed information on both systemically and non-systemically treated patients. It has further agreed to make the results gradually publicly available to provide transparency to all stakeholders concerned. For instance, the funnel plots on toxicity rates of the new drugs increase awareness regarding safety issues in clinical practice. Although no melanoma centre performed significantly worse, the positive outlier (best practice) indicates areas for improvement.

Furthermore, the DMTR may provide information on optimal sequencing of various types of treatment in a real-world setting compared with phase III trials that only report on the investigational drug. This knowledge in combination with data on clinical effectiveness, quality of life, healthcare utilisation, informal care and productivity losses will be used to develop an advanced melanoma disease model. This may provide insight into real-world cost-effectiveness of treatments and treatment patterns, which is increasingly important to ensure the sustainability of the healthcare system. Effectiveness studies are important to both patients and healthcare providers as they determine whether interventions work in the real world, and therefore inform both clinical decision-making and health policy [20].

The DMTR also has its limitations. Population-based registers are generally more prone to registration bias because data are often self-reported and no standardised and uniform criteria are formulated as in clinical trials. This may have led unintentionally to adverse events being less strictly categorised. However, because of the prospective nature of the DMTR's long-term follow-up, patient records are updated every 3 months. To ensure high-quality data, data managers were extensively trained

and oncologists supervise the registration process and validate all data at patient level.
The multipurpose design makes the DMTR an extensive registry raising concerns on the financial and administrative burden and its sustainability in the future. The rough cost per patient in the DMTR is approximately V500, based on an average of 8 hours of registration per patient record, including data-entry (majority of the costs), validation, data-analyses, reporting and training of the data managers. This is a considerable amount; however, in comparison with the price of the drugs per patient, it is not more than 0.5e1% of the total costs per treated patient. Probably, this is an overestimation because costs of hospital resource use and informal care are not even included. It will be important to decision-makers whether securing a small percentage of the total treatment budget for obtaining quality information is acceptable.

Of course it is important to try to reduce the costs of the data registration. In the near future, the DMTR needs to discuss which items are essential to be collected on every patient and which items should be additional; for example, for evaluating cost-effectiveness.
Furthermore, integration with the electronic health record as well as data-linkage with existing sources and registries could reduce the administrative and financial burden even further.

To our knowledge, the DMTR is the first comprehensive population-based registry in advanced melanoma, since BRAF inhibitors and immune checkpoint inhibitors were introduced. The quality performance indicators demonstrated the safe introduction of the new drugs in the Netherlands with toxicity rates that were consistent with the phase III trials conducted. Bearing in mind the increasing number of expensive drugs for cancer coming on to the market, the unique design of the DMTR and the collaboration it represents can be used as a blueprint for future real-world data collection initiatives.

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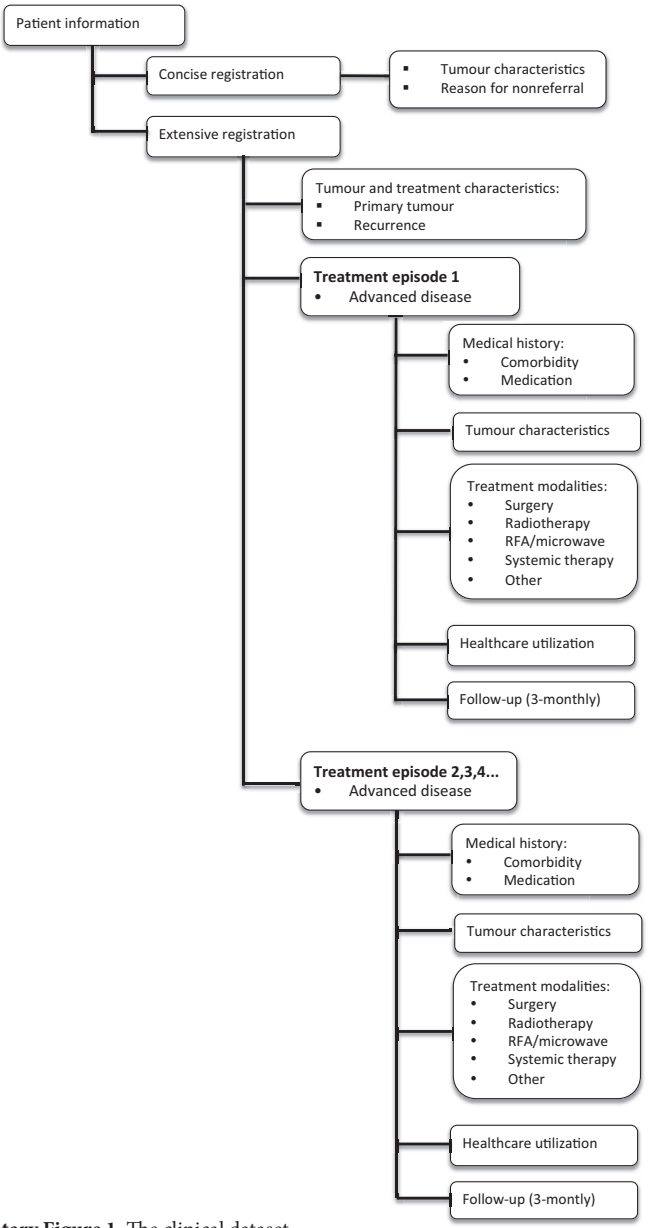
APPENDICES



Supplementary Figure 1. The clinical dataset

4 Vemurafenib in BRAF-mutant metastatic melanoma patients in real-world clinical practice: prognostic factors associated with clinical outcomes

Schouwenburg MG, Jochems A, Leeneman B, Franken MG, van den Eertwegh AJM, Haanen JBAG, van Zeijl MCT, Aarts MJB, van Akkooi ACJ, van den Berkmortel FWPJ, Blokx WAM, de Groot JWB, Hospers GAP, Kapiteijn E, Koornstra RH, Kruit WH, Louwman MWJ, Piersma D, van Rijn RS, Suijkerbuijk KPM, ten Tije AJ, Vreugdenhil G, Wouters MWJM, van der Hoeven JJM

Melanoma Research 2018 Aug;28(4):326-332

ABSTRACT

The aim of this population-based study was to identify the factors associated with clinical outcomes in vemurafenib-treated patients and to evaluate outcomes across subgroups of patients with different risk profiles. Data were retrieved from the Dutch Melanoma Treatment Registry. Time to next treatment (TTNT) and overall survival (OS) of all metastatic melanoma patients who received vemurafenib between 2012 and 2015 were assessed using Kaplan–Meier estimates. A risk score was developed on the basis of all prognostic factors associated with TTNT and OS derived from multivariable Cox regression analyses. Patients were stratified according to the presence of prognostic risk factors by counting the number of factors, ranging from 0 to 6. A total of 626 patients received vemurafenib with a median follow-up of 35.8 months. The median TTNT and OS were 4.7 months [95% confidence intervals (CI): 4.4–5.1] and 7.3 months (95%CI: 6.6–8.0). The strongest prognostic factors were serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group performance score, number of organ sites involved and brain metastases. Patients with a favourable risk profile (no risk factors) had a median TTNT and OS of 7.1 (95%CI: 5.8–8.5) and 15.4 months (95%CI: 10.0–20.9). The median OS more than halved for patients with greater than or equal to 2 risk factors compared with patients with no risk factors. The clinical outcomes of vemurafenib in metastatic melanoma patients with a favourable risk profile are comparable with the results of the trials. Combining prognostic factors into a risk score could be valuable to stratify patients into favourable and poor-prognosis groups.

INTRODUCTION

With the introduction of targeted therapies and immune checkpoint inhibitors, the treatment of metastatic melanoma has been revolutionized [1–6]. The BRIM-3 study showed an improved progression-free and overall survival (OS) of the BRAF inhibitor vemurafenib compared with standard chemotherapy in BRAF-mutant metastatic melanoma [1]. Vemurafenib was the first targeted therapy for metastatic melanoma to be approved by the European Medicines Agency in 2012 [7]. Since then, vemurafenib has increasingly been used in patients with poor prognostic factors as it can induce rapid antitumour response and symptom relief [8].

Patients with poor prognostic factors, such as an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of greater than or equal to 2 and/or symptomatic brain metastases, represent a significant group in real-world clinical practice [9,10], but were excluded from the pivotal trial [1]. Several open-label studies of vemurafenib in metastatic melanoma showed that an ECOG PS greater than or equal to 2, presence of brain metastases and an elevated lactate dehydrogenase (LDH) serum level are among the strongest predictors of impaired outcomes [11,12]. However, there is little evidence on the association of these factors on clinical outcomes in real-world daily practice. Most open-label studies excluded patients with symptomatic brain metastases [11,12] representing over 10% of systemically treated metastatic melanoma patients [13]. Second, the prognostic relevance of combining risk factors has not yet been studied. It is therefore very important to know to what extent the results achieved in the pivotal trials and open-label studies can be extrapolated to real-world melanoma patients treated with vemurafenib.

Furthermore, reliable real-world outcome data of vemurafenib could function as a valuable benchmark for future population-based outcome studies of metastatic melanoma patients treated with the more recently registered drugs, such as concurrent treatment with a MEK and BRAF inhibitor [5], monotherapy or combination therapy with immune checkpoint inhibitors targeting anti-PD1 and/or anti-CTLA-4 [3,6,14]. Therefore, the aim of this population-based study is to identify the prognostic factors associated with clinical out-comes in BRAF-mutant metastatic melanoma patients in real-world clinical practice in The Netherlands. Second, we assessed differences in clinical outcomes across subgroups of patients with multiple prognostic baseline factors.

METHODS

Data: the Dutch melanoma treatment registry

Data were retrieved from the Dutch Melanoma Treatment Registry (DMTR), a population-based registry that was set up to monitor the safety and effectiveness of the new drugs in real-world clinical practice and to assess the quality of melanoma care in The Netherlands. The DMTR registers information on baseline patient and tumour characteristics, treatments, treatment-related adverse events (grade 3 or 4 according to the common terminology criteria for adverse events, version 4) and clinical outcomes of all Dutch patients with unresectable stage IIIc or IV melanoma. A detailed description of the set-up of the DMTR has been published previously [13]. In compliance with Dutch regulations, the DMTR was approved by the medical ethical committee and was not subject to the Medical Research Involving Human Subjects Act.

Patients

All patients with BRAF-mutant unresectable or meta-static (stage IIIc or stage IV) cutaneous melanoma or with a BRAF-mutant melanoma of unknown primary in The Netherlands who received vemurafenib (monotherapy) between 1 July 2012 and 30 June 2015 were included (follow-up data cut-off was 20 November 2016).

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics at the start of vemurafenib treatment. The median time to next treatment (TTNT) and OS with the corresponding two-sided 95% confidence intervals (CI) were analyzed using the Kaplan–Meier method. TTNT is a commonly used measure to assess treatment effectiveness in real-world studies [15] and was determined from the start of vemurafenib to the start of subsequent systemic therapy or death from any cause. The median OS was defined as the time from the start of vemurafenib to the date of death from any cause. Follow-up time was calculated using the inverse Kaplan–Meier method [16]. TTNT and OS were compared between subgroups using log-rank tests for categorical variables and a univariate Cox proportional hazard regression for continuous variables. Subgroups of patients were stratified according to sex, baseline ECOG PS (0, 1, and ≥ 2), baseline LDH level [< 1 × above the upper limit of normal

(ULN) range of 250 U/l, 1–2 × ULN, ≥ 2 × ULN], metastatic stage at baseline (M1a, M1b, and M1c), type of BRAF mutation (V600E, V600K or other), number of organ sites involved at baseline counted as any organ with at least one metastasis (< 3 vs. ≥ 3) and brain metastases at baseline (absent, asymptomatic, or symptomatic). Age was analyzed as a continuous variable.

A backward stepwise multivariable Cox regression analysis was used to identify the baseline prognostic factors associated significantly with OS and TTNT. All factors of the above-mentioned subgroups were entered in the model. Variables with a P value greater than 0.05 were removed from the stepwise model.

A clinical risk score was developed by counting the four prognostic factors of the Cox regression analysis: ECOG PS 0, LDH less than 1 × ULN, no brain metastases and less than 3 organ sites involved counted as 0; ECOG PS 1, LDH 1–2 × ULN and brain metastases counted as 1; and ECOG PS 2 and LDH greater than or equal to 2 × ULN counted as 2. Patients were stratified according to the presence of prognostic risk factors, ranging from 0 to 6.

Missing data were imputed for the Cox regression analyses using multiple imputations by chained equations. To stabilize the results, 10 imputed data sets were produced [17].

All statistical analyses were carried out in PASW Statistics version 20 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient and treatment characteristics

A total of 626 patients with unresectable stage IIIc or IV BRAF-mutant melanoma received vemurafenib from 1 July 2012 until 30 June 2015. The median follow-up was 35.8 months (95%CI: 32–39.5). Most patients had M1c disease (83%), almost one-fifth of patients had an ECOG PS of greater than or equal to 2 (19%) and 19% had symptomatic brain metastases (Table 1). In total, 42% of patients had an elevated serum LDH level. The imputed baseline characteristics were comparable with the observed baseline characteristics (Supplementary Table S1).

Most patients (n = 506; 81%) were treatment naïve. Almost one-fifth received previous systemic therapy (19%), including ipilimumab (6%), chemotherapy (3%),

Table 1. Baseline characteristics of all consecutive patients diagnosed with irresectable melanoma in The Netherlands between July 2012- and July 2015 (n=626) at start of treatment with vemurafenib.

	N (%)
Median age (range), years	59 (23-90)
Age group	
< 50	159 (25)
50-59	157 (25)
60-69	177 (28)
≥70	133 (21)
Gender	
Male	349 (56)
Female	277 (44)
ECOG PS	
0	223 (36)
1	218 (35)
≥2	118 (19)
Unknown	67 (11)
LDH category[a]	
<ULN	343 (55)
≥1 to <2 x ULN	125 (20)
≥2 x ULN	138 (22)
Unknown	20 (3)
Disease stage	
Stage IIIc	12 (2)
M1a	34 (5)
M1b	36 (6)
M1c	522 (83)
Unknown M stage	22 (3)
BRAF mutation	
V600E	505 (81)
V600K	59 (9)
Other	46 (7)
Unknown	16 (3)
Number of organ sites[b]	
<3	215 (35)
≥3	341 (56)
Unknown	58 (9)

Table 1. Baseline characteristics of all consecutive patients diagnosed with irresectable melanoma in The Netherlands between July 2012- and July 2015 (n=626) at start of treatment with vemurafenib. (*continued*)

	N (%)
Brain metastases	
No	394 (63)
Asymptomatic	58 (9)
Symptomatic	119 (19)
Unknown	55 (9)
Previous systemic therapy	
Treatment naive	506 (81)
Previously treated	120 (19)
Median time from advanced melanoma diagnosis to start of vemurafenib (IQR), months	1.4 (0.8-2.8)
Treatment naive	1.2 (0.7-2.1)
Previously treated[c]	6.8 (3.1-12.4)

ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; LDH= lactate dehydrogenase, ULN=upper limit of normal.
[a] ULN is defined at 250 U/L
[b] Patients with stage IV disease (N=613)

dabrafenib (2%), vemurafenib (1%), therapy within a trial (1%) or multiple regimens (7%) (Table 1). At the time of analysis, 95% patients discontinued treatment with vemurafenib, mostly because of disease progression (n = 362; 58%). Other reasons were adverse events (17%), death (8%), preference of the patient (4%), planned in advance (4%) and unknown (10%). Of those who discontinued treatment, 254 (41%) patients received subsequent therapy, including ipilimumab (20%), dabrafenib (9%), anti-PD1 (7%), combination therapy of BRAF and MEK inhibitor (2%), chemotherapy (2%) and retreatment with vemurafenib (1%).

Survival outcomes

The median TTNT and OS were 4.7 months (95%CI: 4.4–5.1) and 7.3 months (95%CI: 6.6–8.0), respectively. Survival rates at 1 and 2 years were 32% (95%CI: 28–35) and 15% (95%CI: 12–18), respectively (Figure 1a and b, Table 2). Table 2 shows the median TTNT, OS and 1-year and 2-year survival rates of the subgroup analyses. Patients with an ECOG PS of greater than or equal to 2 had the lowest

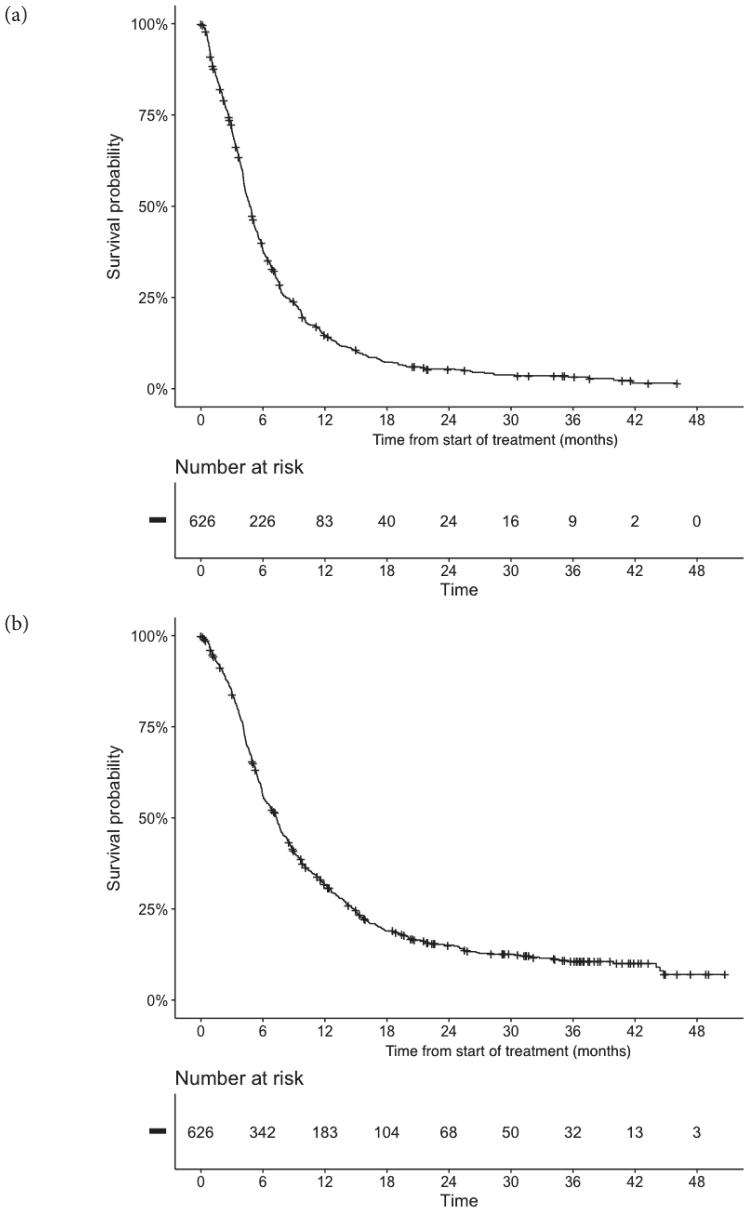


Figure 1. Kaplan–Meier curves of time to next treatment (a) and overall survival (b) of the overall study population.

Table 2. Kaplan-Meier estimates of time to next treatment, median overall survival and 1-year and 2-year survival rates according to prognostic baseline risk factors

Subgroup	*N*	Median TTNT (95%CI), mo	*P*	Median OS (95% CI), mo	1-Year OS (95% CI), %	2-Year OS (95% CI), %	*P*
Age	626	4.7 (4.4-5.1)	0.653	7.3 (6.6-8)	32 (28-35)	15 (12-18)	0.597
Sex							
Male	349	4.8 (4.4-5.3)	0.51	7.2 (6.2-8.2)	31 (26-36)	14 (10-18)	0.932
Female	277	4.7 (4.2-5.2)		7.6 (6.6-8.5)	32 (26-38)	15 (10-19)	
ECOG PS							
0	223	5.5 (4.9-6.1)	<0.001	10.1 (7.9-12.3)	45 (39-52)	21 (15-27)	<0.001
1	218	5.0 (4.5-5.5)		6.7 (5.7-7.7)	25 (19-31)	12 (7-16)	
≥2	118	3.5 (2.9-4.1)		4.1 (3.5-4.6)	13 (7-19)	6 (1-11)	
LDH category							
<ULN	343	5.9 (5.3-6.5)	<0.001	10.0 (8.6-11.5)	42 (37-48)	22 (17-26)	<0.001
≥1 to <2 x ULN	125	4.1 (3.4-4.8)		6.0 (4.8-7.1)	24 (17-32)	6 (1-10)	
≥2 x ULN	138	3.7 (3.3-4.1)		4.4 (3.9-4.9)	8 (3-12)	4 (0-7)	
Disease stage							
IIIc	12	5.5 (0.0-13.9)	<0.001	25.0 (NR-NR)	58 (30-86)	49 (20-78)	<0.001
M1a	34	6.8 (4.8-8.7)		13.8 (11.8-15.9)	63 (47-80)	31 (14-47)	
M1b	36	7.2 (5.0-9.5)		19.9 (12.8-27.0)	67 (51-82)	34 (18-50)	
M1c	522	4.5 (4.2-4.9)		6.4 (5.7-7.0)	26 (22-29)	11 (8-13)	

Table 2. Kaplan-Meier estimates of time to next treatment, median overall survival and 1-year and 2-year survival rates according to prognostic baseline risk factors (*continued*)

Subgroup	*N*	Median TTNT (95%CI), mo	*P*	Median OS (95% CI), mo	1-Year OS (95% CI), %	2-Year OS (95% CI), %	*P*
BRAF mutation							
V600E	501	4.9 (4.5-5.3)		7.4 (6.7-8.2)	34 (29-38)	16 (12-19)	
V600K	59	(4.0 (2.6-5.5)	0.09	5.6 (3.4-7.8)	27 (16-38)	12 (2-22)	0.13
Other	49	4.8 (3.4-6.2)		5.5 (4.4-6.6)	24 (12-37)	11 (1-20)	
No. of organ sites							
< 3	215	5.8 (5.1-6.5)	<0.001	9.7 (7.6-11.8)	42 (36-48)	24 (18-29)	<0.001
≥ 3	341	4.3 (3.9-4.7)		6.1 (5.3-6.8)	24 (20-29)	9 (6-12)	
Brain metastases							
No	394	5.0 (4.4-5.4)		8.4 (7.5-9.2)	36 (31-41)	18 (14-22)	
Asymptomatic	58	4.9 (3.3-6.5)	0.02	7.6 (4.8-10.4)	30 (17-42)	4 (0-10)	<0.001
Symptomatic	119	4.3 (3.7-4.9)		5.4 (4.4-6.3)	17 (10-24)	5 (0-11)	

CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance score, LDH= lactate dehydrogenase, mo= months, NA= not applicable, NR= not reached, OS= overall survival , TTNT = time to next treatment, ULN = upper limit of normal.

median TTNT and OS (3.5 and 4.1 months, respectively) as well as patients with LDH level greater than or equal to 2 × ULN (3.7 and 4.4 months, respectively). The 1-year survival rates were also the lowest in these subgroups of patients. The 1-year survival rate of patients with asymptomatic brain metastases was comparable with that of patients without brain metastases, but decreased considerably to a 2-year survival rate of 5% compared with a 2-year survival rate of 18% for patients without brain metastases. The median OS of patients with previous systemic therapy was not significantly different compared with treatment-naive patients (6.6 months 95%CI: 4.8–8.4 vs. 7.4 months 95%CI: 6.6–8.2, respectively).

Multivariable Cox regression shows that ECOG PS, LDH level and the number of organ sites involved were associated significantly with TTNT and survival (Table 3). The presence of brain metastases was only significantly associated with survival.

Table 3. Multivariable Cox regression analysis of baseline factors associated with overall survival and time to next treatment in patients treated with of vemurafenib

	OS		TTNT	
Covariate	HR (95% CI)[a]	*P*	HR (95% CI)[a]	*P*
ECOG PS				
0	reference		reference	
1	1.5 (1.2-1.8)	<0.001	1.1 (0.9-1.3)	0.304
≥2	2.0 (1.5-2.6)	<0.001	1.7 (1.3-2.1)	<0.001
LDH category				
<ULN	reference		reference	
≥1 to <2 x ULN	1.6 (1.3-2.0)	<0.001	1.7 (1.3-2.1)	<0.001
≥2 x ULN	2.2 (1.8-2.8)	<0.001	1.8 (1.4-2.2)	<0.001
Brain metastases				
No	reference		-	
Asymptomatic	1.2 (0.9-1.6)	0.27	-	-
Symptomatic	1.5 (1.2-1.8)	<0.001	-	-
Number of organ sites				
< 3	reference		reference	
≥3	1.5 (1.2-1.8)	<0.001	1.4 (1.2-1.6)	<0.001

ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; LDH = lactate dehydrogenase; OS = overall survival; TTNT= time to next treatment

[a] Analysis is carried out with an imputed dataset

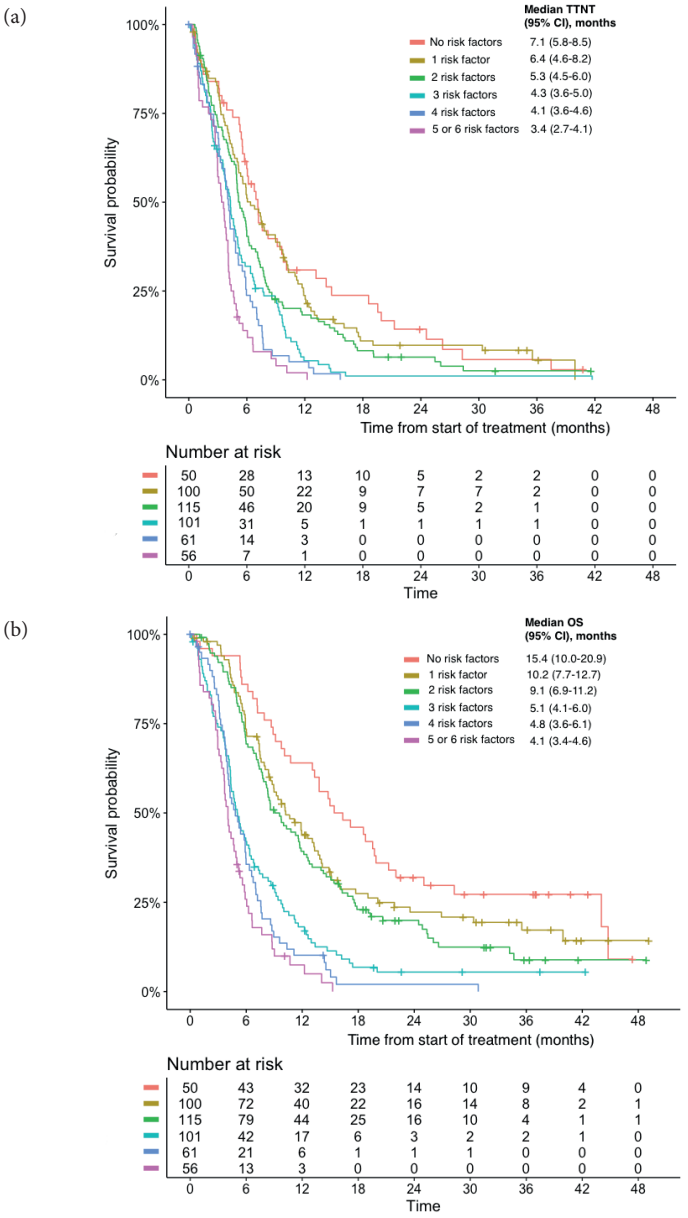


Figure 2. Kaplan-Meier curves of time to next treatment (a) and overall survival (b) according to the number of risk factors at baseline. CI = confidence interval; TTNT = time to next treatment .

A risk score was created with all factors from the multi-variable cox regression, ranging from 0 to 6 factors. Patients with five or six risk factors were merged as only seven patients had six risk factors. Patients with a favourable risk profile (no risk factors; n = 50) had a median TTNT and OS of 7.1 and 15.4 months, respectively (Figure 2a and b). The median TTNT almost halved for patients with four risk factors compared with patients with no risk factors. The median OS decreased considerably for patients with three risk factors compared with patients without any risk factors (5.1 vs. 17.0 months). Patients with five or six risk factors (n = 56) had the lowest median TTNT and OS of 3.4 and 4.1 months, respectively.

DISCUSSION

This study shows that ECOG PS, LDH level and number of organ sites involved were the prognostic factors associated most strongly with TTNT and OS in BRAF-mutant metastatic melanoma patients treated with vemurafenib in real-world clinical practice. We also showed that combining prognostic factors into a clinical risk score could be useful to stratify patients into favourable or poor-prognosis groups.

The median OS in Dutch clinical practice was lower than that reported in the phase III BRIM-3 trial of vemurafenib (7.3 vs. 13.6 months, respectively) [1]. This is most likely because of the relatively large number of patients with less favourable prognostic factors in our population-based study. Over one-third of our study population would have been ineligible for phase III trial enrolment because of symptomatic brain metastases and/or an ECOG PS greater than or equal to 2. Even in the safety study of vemurafenib [11], a lower rate of ECOG PS of greater than or equal to 2 was reported (10 vs. 19% in our study) and patients with symptomatic brain metastases were excluded. The multivariable Cox regression analysis confirmed that both factors impaired survival significantly.

On the basis of the results of our subgroup analyses, the median OS for patients with an ECOG PS greater than or equal to 2 appears to be comparable with survival data reported in the safety study (4.1 vs. 4.9 months, respectively [18]). Similar results were observed for patients with symptomatic brain metastases (5.4 months in our

study vs. 5.1 months in the open-label pilot study of patients with symptomatic brain metastases treated with vemurafenib [19]). Compared with the historic series with an estimated median OS of 2.1 months for patients with brain metastases [20], our study may indicate a benefit of targeted therapy in this subgroup.

Consistent with previous results [11,12], a baseline LDH level of greater than or equal to 2 ULN was an important independent predictor of inferior survival (hazard ratio: 2.2). Although long-term outcomes remain poor, it is known that targeted therapies are capable of inducing rapid antitumour responses and might be more effective in this subgroup compared with immunotherapy [21]. Previous studies on immunotherapies in metastatic melanoma confirmed that benefit was unlikely, reporting a median OS of 2.3 after ipilimumab therapy for patients with an LDH level of greater than or equal to 2 ULN [21] and 2.9 months after anti-PD1 therapy for patients with an LDH level of greater than or equal to 2.5 ULN [22]. Although a direct comparison of outcomes is not possible between studies, our results may indicate more activity of targeted therapy in this patient group. Findings from a pooled analysis of trials of concurrent treatment with a MEK and BRAF inhibitor showed even more promising results for this subgroup of patients with a median OS of 8.8 months [23].

Combining the risk factors instead of assessing them separately could be useful to stratify patients into favourable or poor-prognosis groups and may support clinical-decision making. The median TTNT and OS of 7.1 and 15.4 months in patients with a favourable risk profile (no risk factors) could indicate that durable benefit is possible with vemurafenib in well-defined patient subgroups. However, the majority of patients had one or more risk factors, with almost 70% of patients having multiple risk factors (≥2). The poor outcomes in patients with an unfavourable risk profile (≥3 risk factors; median OS of <5 months) underline the unmet medical need for patients with multiple risk factors treated with vemurafenib monotherapy. In recent years, concurrent treatment with a MEK and BRAF inhibitor has become the standard of care for BRAF-mutant metastatic melanoma patients, including for patients with poor prognostic factors. It will be important to assess whether the superior efficacy achieved in the trials of combined targeted therapies [5,24] may also be achieved in these high-risk groups in daily practice.

This population-based study has some limitations. Registries are generally more prone to missing data compared with clinical trials. The clinical risk score could not be calculated for 23% of patients because data were missing on one or more of the selected risk factors. However, reliable survival data could still be analyzed because of the large sample size and long follow-up. Furthermore, data managers were trained extensively and medical oncologists supervise the registration process to ensure high-quality data [13]. This study only focused on the clinical outcomes TTNT and OS. As vemurafenib is commonly used for symptom relief in unfit patients with a high disease load, the emphasis is predominantly on improving the quality of life. The DMTR is currently collecting quality of life data and we are planning to assess the overall benefit of vemurafenib treatment, especially in patients with poor prognostic factors.

Conclusion

In conclusion, our results show that the clinical outcomes of vemurafenib in BRAF-mutant metastatic melanoma patients with a favourable risk profile are comparable with the pivotal trials. However, our results also emphasize that trial results are not generalizable to a more heterogeneous patient population in daily practice as the majority of patients have a less favourable risk profile. Real-world data from clinical practice complement the knowledge on clinical outcomes in high-risk metastatic melanoma patients, in particular, on patients with multiple risk factors.

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APPENDICES

Supplementary Table 1. Imputed baseline characteristics of patients treated with vemurafenib

	Real-world data *N*= 626 *N* (%)	Imputed data *N*= 626 *N* (%)
Median age (range), years	59 (23-90)	59 (23-90)
Age group		
< 50	159 (25)	159 (25)
50-59	157 (25)	157 (25)
60-69	177 (28)	177 (28)
≥70	133 (21)	133 (21)
Sex		
Male	349 (56)	349 (56)
Female	277 (44)	277 (44)
ECOG PS		
0	223 (40)	248 (40)
1	218 (39)	244 (39)
≥2	118 (21)	134 (21)
Unknown	67 (11)	
LDH category[a]		
<ULN	343 (57)	347 (55)
≥ULN	263 (43)	279 (45)
≥1 to <2 x ULN	125 (21)	130 (21)
≥2 x ULN	138 (23)	149 (24)
Unknown	20 (3)	
Disease stage		
Stage IIIc	12 (2)	12 (2)
M1a	34 (6)	35 (6)
M1b	36 (6)	37 (6)
M1c	522 (86)	542 (87)
Unknown M stage	22 (3)	
Number of organ sites[b]		
<3	215 (39)	238 (37)
≥3	341 (61)	387 (63)
Unknown	58 (9)	

Supplementary Table 1. Imputed baseline characteristics of patients treated with vemurafenib (*continued*)

	Real-world data *N*= 626 *N* (%)	Imputed data *N*= 626 *N* (%)
Brain metastases		
No	406 (70)	437 (70)
Asymptomatic	58 (10)	62 (10)
Symptomatic	119 (20)	127 (20)
Unknown	43 (7)	
Previous systemic therapy		
Treatment naive	506 (81)	506 (81)
Previously treated	120 (19)	120 (19)

yrs=years; PS = performance score; LDH= lactate dehydrogenase, ULN=upper limit of normal.
[a] ULN is defined at 250 U/L
[b] Patients with stage IV disease (N=614)

5 Early switching of targeted therapy to immunotherapy; the road to long-term survival in LDH elevated advanced melanoma patients?

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Submitted

ABSTRACT

Background: The clinical outcomes of advanced BRAF-mutant melanoma patients with elevated serum lactate dehydrogenase (LDH) remain very poor. The aim was to explore whether patients with normalized LDH after targeted therapy could benefit from subsequent immunotherapy.

Methods: Data from all BRAF-mutant metastatic melanoma patients with an initial elevated serum LDH (≥ 2x above the upper limit of normal) receiving first-line targeted therapy between 2012 and 2017 in The Netherlands were prospectively collected. Patients were stratified according to response status to targeted therapy and change of LDH at start of subsequent immunotherapy. Differences in overall survival (OS) between the subgroups were compared using log-rank tests.

Results: After a median follow-up of 22.1 months, median OS of the total study population (N=270) was 4.7 months (95% CI 4.3– 5.1). Of all patients receiving subsequent immunotherapy (N=65), survival from start of subsequent immunotherapy was significantly longer in patients who had normalized LDH and were still responding to targeted therapy compared to those with LDH that remained elevated (median OS not reached vs 0.9 months).

Conclusions: Introducing immunotherapy upon response to targeted therapy with normalization of LDH could be an effective strategy in obtaining long-term survival in metastatic melanoma patients with elevated serum LDH.

INTRODUCTION

Multiple effective systemic treatment options have emerged for patients with advanced BRAF-mutant melanoma over the last decade. Since the approval of the BRAF inhibitor vemurafenib [1] and the CTLA-4 antibody ipilimumab [2], combination therapy with a BRAF and MEK inhibitor [3] and treatment with anti-PD-1 antibodies as monotherapy [4] [5] or combined with a CTLA-4 antibody [6] have broadened the therapeutic arsenal for these patients. Combination therapy with a BRAF and MEK inhibitor has resulted in a median overall survival of over 2 years [7], while treatment with anti-PD-1 also concurrently showed significant improvements with 2-year survival rates of 55-58% [8]. Although long-term survival may be achieved in a subgroup of patients, there is still an unmet medical need for patients with unfavourable prognostic factors [9][7]. Elevated serum lactate dehydrogenase (LDH) level is a well-known marker for poor outcome and a strong negative predictor for response to immunotherapy and targeted therapy [7][8]. In previous reports substantially less activity was demonstrated in patients with elevated serum LDH of ≥2x upper limit of normal (ULN), with a median OS of 2.9 months after ipilimumab therapy [9] and 2.3 months after anti-PD1 therapy [10] compared to 14.7 months and 16.1 months for patients with normal LDH, respectively. Similarly, LDH has been shown to be one of the key predictors of survival for patients receiving targeted therapy [11]. Although the majority of BRAF mutant patients with elevated serum LDH respond to targeted therapy, responses are usually short-lived, with median progression-free survival shorter than 6 months for patients with LDH ≥2xULN compared to 17 months for the patients with normal LDH [7].

Targeted therapies are capable of inducing rapid anti-tumour responses associated with a decrease in LDH [7], which might enable immunotherapy to work more efficiently in patients with initial elevated serum LDH. Furthermore, BRAF and MEK-inhibition could facilitate immune responses in multiple ways. Preclinical data showed an increase in CD8+ T-cell recognition of tumour cells by inducing rapid upregulation of MHC class I surface expression in BRAF-mutant melanoma cells [12] [13]. These data support the potential of BRAF-inhibition to increase response rates to immunotherapy. Although this concept seems promising, clinical data supporting the approach of BRAF inhibitor induction treatment preceding immunotherapy in

patients with aggressive disease are lacking and little is known about which patients could benefit from induction treatment.
This prospective population-based study focuses on the clinical outcomes of BRAF mutant metastatic melanoma patients with baseline serum LDH of ≥2x ULN treated with first-line targeted therapy. The main objective of the study was to investigate whether the level of LDH and response status at the switch to immunotherapy was associated with survival.

METHODS

Data: the Dutch Melanoma Treatment Registry (DMTR)

Data was retrieved from the Dutch Melanoma Treatment Registry (DMTR), a prospective population-based registry that was set-up to monitor the safety and effectiveness of the new drugs in real-world clinical practice and to assess the quality of melanoma care in the Netherlands. The DMTR contains information on baseline patient and tumour characteristics, local and systemic treatment modalities, treatment-related adverse events (grade 3 or 4 according to common terminology criteria for adverse events (CTCAE) version 4) and clinical outcomes of all patients with unresectable stage IIIc or IV melanoma. A detailed description of the DMTR was published previously [14].
In compliance with Dutch regulations, the DMTR was approved by the medical ethical committee and was not subject to the Medical Research Involving Human Subjects Act. Patients were offered an opt-out option.

Patients

All patients with BRAF-mutant unresectable or metastatic (stage IIIC or stage IV) cutaneous melanoma or with a BRAF-mutant melanoma of unknown primary with a baseline serum LDH of ≥2x above the upper limit of normal (ULN) who received targeted therapy (either monotherapy with a BRAF inhibitor or combination therapy with BRAF and MEK inhibitors) between July 1st 2012 and June 30th 2017 were included (follow-up data cut-off was November 5th 2017). The ULN was defined at 250 U/L. Patients with prior systemic treatment for metastasized disease were excluded to avoid bias of on going activity of previous systemic agents.

Statistical analysis

Time to next treatment (TTNT) and overall survival (OS) with corresponding two-sided 95% confidence intervals (CI) for medians were analysed using the Kaplan-Meier method. For the overall study population, TTNT was determined from the start of targeted therapy to the start of subsequent systemic therapy or death from any cause. Patients who were still on treatment were censored at time of analysis. OS was defined as the time from start of targeted therapy to the date of death from any cause. Patients alive at time of analysis were censored. Follow-up time was calculated from start date of targeted therapy using the inverse Kaplan-Meier method [15].

The main objective of the study was to investigate whether the response to targeted therapy and level of serum LDH at start of subsequent immunotherapy affects survival. For this analysis, OS was defined from start of subsequent immunotherapy to the date of death from any cause. Patients were stratified according to LDH at start of subsequent immunotherapy (< ULN, >1 to < 2x ULN, ≥2x ULN) and tumour response after treatment of targeted therapy according to Response Evaluation Criteria in Solid Tumors (RECIST). OS was compared between the subgroups using log-rank tests. Multivariable Cox proportional hazard model was applied to identify prognostic factors at start of subsequent immunotherapy associated with OS. Backward stepwise selection was performed to eliminate non-influential variables from the multivariable model. The following factors at start of immunotherapy were entered in the model: gender, age, ECOG PS (0,1 and ≥2), serum LDH (<1x ULN, 1-2x ULN, ≥2x ULN), number of organ sites involved counted as any organ with at least one metastasis (<3 *vs* ≥ 3), brain metastases (no brain metastases, asymptomatic, symptomatic), RECIST response on targeted therapy. Statistical significance was defined as a two-sided p value <0.05.

All statistical analyses were performed in PASW Statistics version 20 (SPSS Inc. Chicago, IL).

RESULTS

Overall study population

A total of 4043 unresectable stage IIIC or IV melanoma patients were registered in the DMTR between July 1st 2012 and June 30th 2017 (Supplemental Figure 1). Of

Table 1. Patient and treatment characteristics of study population

	N=270 (%)
Median age, years (IQR)	60 (59-88)
Age in categories	
<50	67 (25)
50-59	65 (24)
60-69	79 (29)
≥70	59 (22)
Gender	
Male	163 (60)
Female	107 (40)
ECOG PS	
0	63 (23)
1	78 (29)
≥2	99 (37)
Unknown	30 (11)
Median baseline LDH (IQR)	815 (613-1396)
Nubmer of organ sites involved	
<3	49 (18)
≥3	195 (72)
Unknown	26 (10)
Brain metastases	
No	186 (69)
Asymptomatic	24 (9)
Symptomatic	43 (16)
Unknown	17 (6)
Type of targeted therapy	
BRAFi monotherapy	205 (76)
BRAFi + MEKi	65 (24)
Type of subsequent immunotherapy	
Ipilimumab	23 (9)
Anti-PD1	29 (11)
Ipilimumab & nivolumab	14 (5)

IQR = interquartile range; ECOG PS = Eastern Cooperative Oncology Group performance status; BRAFi = BRAF-inhibitor; MEKi= MEK inhibitor

these, 270 BRAF-mutant advanced melanoma patients with a baseline serum LDH of ≥2x ULN received first-line targeted therapy and were included for analyses. Baseline characteristics are shown in Table 1. The median age was 60 years and the majority of patients were male (60%). Median serum LDH was 815 U/L (IQR 613-1396). Thirty seven percent of patients had an ECOG PS of ≥2 and most patients had ≥3 organ sites involved (72%). The majority of patients received BRAF monotherapy (76%). BRAF monotherapy was administered up to August 2016. Combination therapy with a BRAF- and MEK inhibitor was increasingly being used since October 2015 and was the only administered therapy in 2017. Median follow-up was 22.1 months (95% CI 14.8- 29.5) and 228 patients (84%) died during follow-up. At time of analysis, 93% of patients discontinued treatment with targeted therapy, due to disease progression (63%), toxicity (10%) and death (10%), planned in advance (7%), patient's choice (2%), other (4%) and unknown (4%).

Median OS was 4.7 months (95% CI 4.3– 5.1) (Figure 1). Survival rates at 6 months and 1 year were 37% (95%CI 31-43) and 12% (95% CI 8-16), respectively.

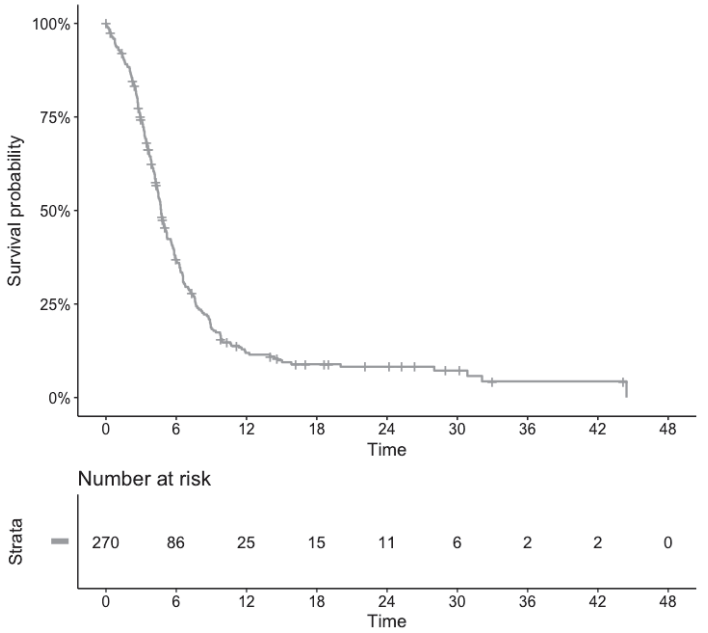

Figure 1. Overall survival of study population.

Table 2. Patient and treatment characteristics at start of subsequent immunotherapy

	N=65 (%)
Median age, years (min-max)	56 (16-77)
Age in categories	
<50	18 (28)
50-59	17 (26)
60-69	18 (28)
≥70	12 (18)
Gender	
Male	43 (66)
Female	22 (34)
ECOG PS	
0	12 (18)
1	37 (57)
≥2	7 (11)
Unknown	9 (14)
Number of organ sites involved	
<3	11 (17)
≥3	48 (74)
Unknown	6 (9)
Brain metastases	
No	46 (71)
Asymptomatic	9 (14)
Symptomatic	7 (11)
Unknown	3 (3)
Type of targeted therapy	
BRAFi monotherapy	41 (63)
BRAFi + MEKi	24 (37)
Serum LDH	
<ULN	19 (29)
≥1 to <2 x ULN	27 (42)
≥2 x ULN	19 (29)
Response on targeted therapy	
Partial response	7 (11)
Stable disease	6 (9)
Progressive disease	52 (80)

ECOG PS = Eastern Cooperative Oncology Group performance status; BRAFi = BRAF-inhibitor; MEKi= MEK inhibitor. LDH= lactate dehydrogenase, ULN=upper limit of normal.

Patients with subsequent immunotherapy

A total of 65 patients (24%) received subsequent immunotherapy. Anti-PD1 (44%) was most often administered, followed by ipilimumab (35%) and a combination of ipilimumab & nivolumab (21%). Baseline characteristics at start of subsequent immunotherapy are shown in Table 2. Median follow up from start of subsequent immunotherapy was 15.0 months (95% CI 5.7- 24.4).

Outcomes were stratified according to LDH at start of subsequent immunotherapy and tumour response after targeted therapy. Table 3 shows the median OS and 6-months survival rates, calculated from start of subsequent immunotherapy.

Patients with a normalized LDH who had a partial response to targeted therapy (BRAF monotherapy: n=5, combination therapy with BRAF and MEK inhibitor: n=1) had the best survival from start of immunotherapy (median OS and 6-months survival rate not reached). These patients had an original LDH level at start of targeted therapy between 541- 690 U/L. Median duration of targeted therapy before switching to immunotherapy was 2.4 months (95%CI 2.2-2.7).

All patients who had an elevated LDH at start of immunotherapy had progressed on targeted therapy (n=44). Median duration of targeted therapy before switching to

Table 3. Kaplan-Meier estimates of time to next treatment, median overall survival, and 6 months survival rates at start of subsequent immunotherapy, according to serum LDH at start of subsequent immunotherapy and tumour response after targeted therapy

Serum LDH at start IT	Response on targeted therapy	Deaths/ No. of patients	Median OS (95% CI), mo	6 mo survival rate (95% CI), %
<ULN				
	PR	0/6	NR	NR
	SD	4/5	8.8 (0-20.9)	60 (17-100)
	PD	7/8	4.4 (2.4-6.3)	29 (0-62)
≥1 to <2x LN[a]				
	PD	19/25	2.7 (1.9-3.6)	22 (5-39)
≥2 x ULN				
	PD	16/19	0.9 (0.3-1.7)	17 (0-34)

LDH= lactate dehydrogenase, ULN=upper limit of normal, IT = immunotherapy, TTNT = time to next treatment, OS = overall survival, mo = months, NR = not reached, PR = partial response, SD = stable disease, PD = progressive disease.

[a] Due to low numbers of patients with stable disease (N=1) and partial response (N=1) in this subgroup, these patients were excluded from analyses

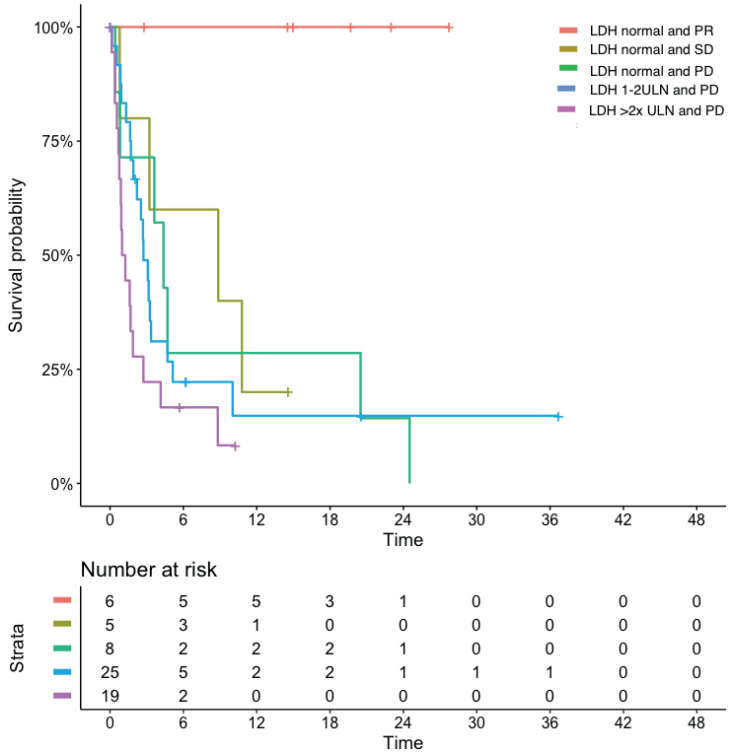

Figure 2. Kaplan Meier curves of overall survival at start of subsequent immunotherapy, according to serum LDH at start of subsequent immunotherapy and tumour response after targeted therapy.

immunotherapy was 5.8 months (95%CI 4.7-6.9). Patients who started second-line immunotherapy with LDH ≥2x ULN had the worst outcomes with a median OS of 0.9 months (95%CI 0.3-1.7) and 6-months survival rate of 17% (95%CI 0-34). The survival curves demonstrate significant survival differences between the normalized LDH group with partial response compared to the other subgroups (Figure 2).

After backward multivariable selection, only LDH at start of second-line immunotherapy and response to targeted therapy retained in the final model (Table 4). In particular, normal LDH was significantly associated with survival (HR 0.38 95%CI 0.16-0.94). No significant differences were found between characteristics at start of second-line immunotherapy according to response status to immunotherapy (data not shown).

Table 4. Multivariable Cox regression analysis after backward stepwise selection associated with overall survival using baseline characteristics at start of immunotherapy.

	OS HR (95% CI)	*P*
Response on targeted therapy		
PR	0.24 (0.05-1.07)	0.061
SD	0.64 (0.23-1.77)	0.391
PD	reference	
LDH level at start of immunotherapy		
<ULN	0.38 (0.16-0.94)	0.036
≥1 to <2 x ULN	0.50 (0.25-1.02)	0.058
≥2 x ULN	reference	

LDH= lactate dehydrogenase, ULN=upper limit of normal, IT = immunotherapy, OS = overall survival, HR = hazard ratio, PR = partial response, SD = stable disease, PD = progressive disease.

DISCUSSION

These real-world data support previous reports of the poor prognosis of advanced melanoma patients with elevated serum LDH. At the same time, these data provide a potential strategy to improve clinical outcomes. In our cohort of metastatic melanoma patients with baseline serum LDH of ≥ 2x ULN treated with first-line BRAF(/MEK) inhibitors, median OS was significantly longer in patients who started second-line immunotherapy with normalized LDH and still responding to initial targeted therapy compared to those with elevated LDH at start of immunotherapy. Our data suggest that introducing immunotherapy upon response to targeted therapy with normalization of LDH could be an effective strategy in obtaining long-term survival in patients with initial elevated serum LDH.

The median OS of 4.7 months of the overall study population confirms previous data that clinical outcomes remain poor in this subgroup of patients [9] [10] [16]. Patients who received subsequent immunotherapy with LDH ≥ 2x ULN at start of immunotherapy are unlikely to benefit from immunotherapy with a median OS of 0.9 months and a 6-months survival rate of 17%.

The exact role of LDH is not completely elucidated. It could simply be a marker of more aggressive disease that requires rapid anti-tumour responses [9]. The delayed

tumour responses generally observed with immunotherapies might therefore take too long for these patients to benefit. Moreover, tumour metabolism is characterized by the conversion of pyruvate into lactate, even in the presence of sufficient oxygen. Preclinical data demonstrated that tumour cells producing high levels of lactic acid disturb the function of cytotoxic T lymphocytes, thereby negatively influencing the potency of an immune response [17] [18].

Interestingly, our data showed that patients who switch to immunotherapy with normalized LDH while still responding to targeted therapy have a real chance of long-term survival. After a median follow-up of 15 months, median OS was not reached and survival was significantly longer compared to the other subgroups. Moreover, targeted therapy was given as an 'induction' therapy with a median duration of only 2.4 months, suggesting that sequential treatment with an early switch to immunotherapy in this subgroup could result in durable outcomes. Although promising, baseline LDH values of these patients did not exceed 690 U/L (<3x ULN). Patients with extremely high LDH values of >3x ULN at baseline might not be good candidates for this strategy. It should also be noted that only a small proportion of patients received this treatment strategy (n=6; 2%). However, the majority of our study population received BRAF monotherapy as first-line targeted therapy. The emergence of combination therapy with a BRAF and MEK inhibitor for this subgroup of patients might lead to a greater proportion of patients with response to targeted therapy and normalisation of LDH. A 3-year follow-up pooled analysis of phase III trials with BRAF and MEK inhibitor combination therapy showed promising results with 50% partial response in patients with initial LDH ≥ 2x ULN [19].

The value of sequencing targeted therapy prior to immunotherapy in patients with initial elevated LDH has not been investigated thus far. Previous retrospective reports revealed that normalization of LDH while on targeted therapy was a strong feature of ipilimumab cycle completion [20] [21]. Another report on 101 advanced melanoma patients with decreased serum LDH after BRAF inhibitor treatment who were fit enough to complete all courses of ipilimumab had a significantly longer OS compared to those who did not (median OS 12.7 months *vs* 1.2 months) [22].
The real benefit of induction treatment with combined BRAF- and MEK-inhibition in patients with elevated LDH is currently investigated in multiple prospective ran-

domized trials. In the Netherlands, the phase II COWBOY study (NCT02968303) comparing BRAF- and MEK-inhibitor induction treatment with vemurafenib and cobimetinib followed by ipilimumab and nivolumab or upfront immunotherapy in advanced melanoma patients with elevated serum LDH is currently recruiting. Another trial, the EORTC EBIN study (NCT03235245), will compare ipilimumab and nivolumab upfront versus the same treatment preceded by induction therapy with encorafenib and binimetinib in advanced melanoma patients, irrespective of LDH level. One of the arms of the three-arm phase II SECOMBIT study (NCT02631447) will assess whether an induction treatment with encorafenib plus binimetinib of 8 weeks before combination immunotherapy might help potentiate an immunotherapeutic response. Guidelines are not conclusive on this issue and the abovementioned trials are currently recruiting. Our results may therefore be of added value to medical oncologists while awaiting these trial results.

It would be interesting to investigate survival differences between patients who started second-line immunotherapy with normalized LDH and response to initial targeted therapy vs responders who stayed on targeted therapy. The 3-year follow-up pooled analysis of phase III trials with BRAF and MEK inhibitor combination therapy showed that patients with initial elevated LDH levels that normalized at 6 months could have long-term benefit with a 3-years survival rate of 41% [19]. Unfortunately, this could not be assessed with our data, as we have no information of LDH level during follow-up of patients who stayed on targeted therapy.

Given the observational design of this analysis, we cannot rule out confounding by indication or selection bias. However, its multicentre design attenuates this potential selection bias. Furthermore, observational studies are more susceptible to registration bias. To ensure high-quality data, data managers were extensively trained and supervised by oncologists [14]. Another limitation is the small number of patients of the subgroup analyses. The conclusions drawn need validation in prospective randomized trials. Lastly, other clinical parameters such as lymphocyte counts and CRP level that have also been associated with patient outcome after immunotherapy were not registered in our database and could therefore not be included in this study [18].

In conclusion, our population-based study suggests immunotherapy upon response to targeted therapy with normalization of LDH may be beneficial in this group of patients with generally a poor prognosis. Nevertheless, randomized trials are needed to assess the real benefit of sequential treatment of targeted therapy and immunotherapy in patients with elevated serum LDH.

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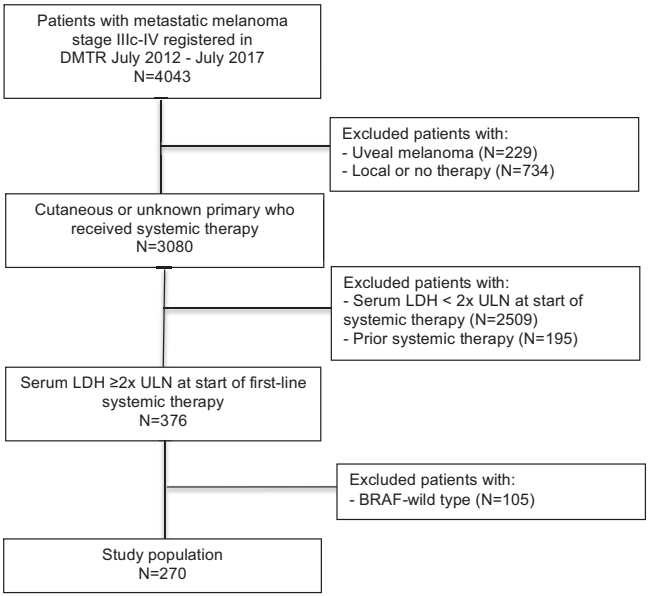
APPENDICES



Supplementary Figure 1. Flowchart of study population

Part III

Assuring quality focusing on patient centred outcomes

6 An international collaborative standardizing a comprehensive patient centered outcomes measurement set for colorectal cancer

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JAMA Oncol 2017 May 1;3(5):686-694

ABSTRACT

Importance: Global health systems are shifting toward value-based care in an effort to drive better outcomes in the setting of rising health care costs. This shift requires a common definition of value, starting with the outcomes that matter most to patients.

Objective: The International Consortium for Health Outcomes Measurement (ICHOM), a non-profit initiative, was formed to define standard sets of outcomes by medical condition. In this article, we report the efforts of ICHOM's working group in colorectal cancer.

Evidence review: The working group was composed of multidisciplinary oncology specialists in medicine, surgery, radiation therapy, palliative care, nursing, and pathology, along with patient representatives. Through a modified Delphi process during 8 months (July 8, 2015 to February 29, 2016), ICHOM led the working group to a consensus on a final recommended standard set. The process was supported by a systematic PubMed literature review (1042 randomized clinical trials and guidelines from June 3, 2005, to June 3, 2015), a patient focus group (11 patients with early and metastatic colorectal cancer convened during a teleconference in August 2015), and a patient validation survey (among 276 patients with and survivors of colorectal cancer between October 15, 2015, and November 4, 2015).

Findings: After consolidating findings of the literature review and focus group meeting, a list of 40 outcomes was presented to the WG and underwent voting. The final recommendation includes outcomes in the following categories: survival and disease control, disutility of care, degree of health, and quality of death. Selected case-mix factors were recommended to be collected at baseline to facilitate comparison of results across treatments and health care professionals.

Conclusions: A standardized set of patient-centered outcome measures to inform value-based health care in colorectal cancer was developed. Pilot efforts are under way to measure the standard set among members of the working group.

INTRODUCTION

Colorectal cancer (CRC) is the third leading cancer in men and the second leading cancer in women globally, with 1.2 million new cases and 600 000 deaths per year [1]. Existing treatment options include surgery, radiation therapy, and chemotherapy, each with trade-offs between disease treatment and quality of life (QOL). Within each treatment modality, significant variation exists in the quality of care delivered across institutions, suggesting that there is opportunity for standardization to ensure high-value health care for all patients [2].

Value-based health care is a conceptual framework that is guiding global health system reform and will grow in importance with re-cent health care policy changes [3]. It is founded on the principle of mea-suringandmakingdecisionson-theoutcomesofcarerelativetothetotal cost of care [4]. In this instance, outcomes are patient-centered outcomes that include not only survival but also the ability to lead productive lives free of the symptoms of disease or treatment. Value-based health care is a framework that guides internal improvement efforts and system-level policies, such as reimbursement, market transparency, and comparative effectiveness research [5-7]. The foundation for these efforts is a common definition of value, starting with outcomes.
Outcomes measurement efforts in CRC exist [8,9]. However, to our knowledge, no measurement initiative includes patient-reported out-comes and is accepted internationally. This lack of standardized measurement impedes a widespread attainment of value-based care for patients with CRC. To inform the development of value-based initiatives [10], the International Consortium for Health Outcomes Measurement (ICHOM) secured funding to develop a comprehensive patient-centered outcomes measurement set for this patient group.

METHODS

The development of a standard set was initiated by ICHOM (http: //www.ichom.org). ICHOM is a non-profit organization that has developed standardized sets of pertinent outcomes for multiple medical conditions, including cancers of the prostate

[11,12] and lung [13]. No institutional review board approval or informed consent was required for this study.

Working Group

ICHOM assembled a diverse team of experts (all authors except J. Lippa) and formulated a working group (WG), including representatives from patient advocacy groups, palliative care, oncology nursing, pathology, epidemiology, and radiation, surgical, and medical oncology from Europe, Australia, Asia, and the United States. A smaller project team (PT) (J.A.Z., M.G.S., A.C.M.V., C.S., C.J.V., and R.T.) guided the efforts of the larger group.

Development of the CRC Cancer Standard Set

The WG convened via 8 teleconferences between July 8, 2015, and February 29, 2016, and proceeded through a structured process similar to that described for prior cancer standard sets [11,12,14-16]. The development of the standard set involved several phases, shown in detail in the eFigure in the Supplement.

Development of Potential Outcomes List

The PT performed a structured PubMed (June 3, 2005, to June 3, 2015) literature review to identify clinical and patient-reported outcomes and measures of health-related QOL in men and women with CRC (eTable 1). The literature review identified 1042 randomized clinical trials and guidelines. Three individuals (including J.A.Z.) reviewed citations until a saturation of outcomes was observed at 310 citations. Existing CRC registries were also reviewed, and the WG was asked to identify pertinent sources.

An international focus group of 11 patients (including authors D.B., J. Lloyd, P.K.M., and K.R.) with early and metastatic CRC was convened during a teleconference in August 2015. Through a semi-structured interview, participants provided their input on patient-centered outcomes for CRC, including which outcomes mattered most to them or other patients with CRC, what affected them most in day-to-day activities, and during what period. They were asked about outcomes in the categories of survival and disease control, complications, and degree of health. Findings from the literature review and the focus group were used to guide and inform the content of the WG teleconference discussions.

Modified 2-Round Delphi Method to Prioritize Outcomes and Case-Mix Variables

After each teleconference, each WG member voted anonymously for inclusion or exclusion of each outcome or case-mix variable. A similar process was used to agree on outcome definitions or, in the case of patient-reported outcomes measurements (PROMs), the measurement tool to be recommended.

Two rounds of a modified Delphi process were conducted. As per prior outcome development [17-19], inclusion for all proposed out-comes and case-mix variables required consensus by at least 70% of the WG members rating the item as very important (score of 7-9 on a 9-point Likert-type scale) in either round (eTable 2 and eTable 3). The items had to score between 7 and 9 by at least 50% to 70% in the second voting round to be brought to a final vote. The items were included in the standard set when at least 70% of WG members voted for inclusion in this final vote. Members of ICHOM maintained the data and conducted the surveys, but neither ICHOM nor its funders influenced voting.

Validation of Outcomes

The final list of outcomes as defined by the WG was validated in a larger group of patients with and survivors of CRC. Patients were recruited via several CRC patient organizations (Bowel Cancer Australia, Colon Cancer Alliance, Fight Colorectal Cancer, and the Association of Cancer Online Resources Colon Discussion List) to complete an anonymous online survey. Through social media recruitment, participants were asked to rate the importance of out-comes on a 9-point Likert-type scale. Participants had the option of including additional missing outcomes in a free-text box (eTables 4, 5, and 6).

PROM Tools Selection

After finalizing the list of outcomes, the corresponding PROMs were identified. The PROMs' psychometric qualities were evaluated by the PT according to the International Society for Quality of Life Research Standards (eTable 7) [20]. A mapping of outcomes to PROMs was presented to guide WG members in decision making (eTable 8).

External Input

The final standard set was presented to key stakeholders and others with an interest in outcomes measurement to review the set and provide feedback via an online survey. They were asked to rate their confidence on a 9-point Likert-type scale on several elements of the set (eg, completeness of the outcomes list and implementation feasibility), with an open field for comments (eTable 9).

RESULTS

Project Scope

The PT defined the scope of the project as all patients with invasive, American Joint Committee of Cancer stage I to IV colon or rectal cancer regardless of type or intent of treatment received, including those who did not receive therapy. Patients undergoing treatment with investigational agents were excluded because such studies have their own specific outcome assessments.

Outcomes

After consolidating findings of the literature review and focus group meeting, a list of 40 outcomes was presented to the WG and underwent voting (eTable 2). Outcomes were grouped into the following 4 categories: survival and disease control, disutility of care (short-term treatment complications), degree of health (QOL, functioning, and long-term adverse effects), and quality of death. The final 31 outcomes are listed in Table 1 and are discussed below. Of the 276 patients participating in the patient validation survey between October 15, 2015 and November 4, 2015, 223 (80.8%) believed that this list captured the most important outcomes and that no additional outcomes had to be included (eTable 6). Some respondents suggested additional outcomes, which are discussed below. The timeline for outcome assessment was determined by the WG to achieve a balance between the clinically relevant times when outcomes may be expected to change and the pragmatic concerns that institutions and practices face in data collection (Figure 1).

Table 1 – Summary of outcomes for the ICHOM Colorectal Cancer Standard Set

Patient Population	Measure	Details	Data Sources[a]
Survival and Disease Control			
All patients	Overall survival	Date of death	Administrative data (death registry/claims data)
	Cause of death	Death attributed to colorectal cancer	
Patients with curative intent	Recurrence free survival	Local, regional or distant recurrence	Clinical abstraction
Patients with advanced disease	Progression free survival	Disease progression	
Patients with rectal cancer receiving neo-adjuvant therapy	Pathologic or clinical complete response	No sign of residual invasive cancer of resected specimen or on diagnostic evaluation	
Patients with rectal cancer receiving surgery	Margin status	Evidence of circumferential margin involvement	
Disutility of Care			
All patients with treatment	Short-term complications of treatment[b]	Any complication leading to: An intervention Prolonged hospitalization Unplanned readmission Intensive care (unit) management Discontinuation of treatment Reduced dosing Limiting self-care ADL[c] Death	Clinical abstraction
Degree of Health			
All patients	Overall well-being	Tracked via EORTC QLQ-C30	Patient-reported sources
	Physical functioning		
	Emotional functioning		
	Social functioning		
	Mobility		
	Depression		
	Pain		
	Fatigue		

Table 1 – Summary of outcomes for the ICHOM Colorectal Cancer Standard Set (*continued*)

Patient Population	Measure	Details	Data Sources[a]
	Sexual functioning	Tracked via EORTC QLQ-CR29	
	Bowel functioning		
Patients with surgery/ radiotherapy	Dietary issues	Tracked via MSKCC Bowel Function - Dietary Subscale	
	Fecal leakage	Tracked via EORTC QLQ-CR29	
	Stool frequency		
	Diarrhea		
	GI symptoms		
	Erectile dysfunction		
	Vaginal symptoms		
Patients with systemic therapy	Neuropathy	Tracked via EORTC QLQ-LMC21- one item	
Patients with surgery	Presence of stoma (colostomy/ileostomy	If yes, report ostomy functioning as well via EORTC-QLQ-CR29	Clinical and, if applicable, patient-reported
Quality of Death			
Patients with advanced disease	Hospital admission at the end of life	Admission to the hospital > 1 time in last 30 days of life	Clinical abstraction
	Hospice care	Hospice care at time of death	Administrative or clinical abstraction
	Place of death	Where patient died (home, hospital, nursing home/care home)	Administrative data (death registry/claims data)
	Preference for place of death	Where patient preferred to die (home, hospital, nursing home/care home)	Clinical abstraction

EORTC= European Organization for Research and Treatment of Cancer, MSKCC = Memorial Sloan Kettering Cancer Center, CTCAE= US National Cancer Institute Common Terminology Criteria for Adverse Events, N/A = not applicable

[a] The data source reflects the way outcomes are collected and was determined as clinical (e.g. physician report), patient-reported (e.g. EORTC QLQ C-30) or administrative (with a combination of ways in some cases)

[b] Collection of short-term complications is recommended whilst the patient is undergoing treatment or within 90 days after initiation of treatment. The type of acute complication is also to be recorded, specific to treatment type (surgery: leakage, breakdown of anastomosis, wound infection, thrombo-

embolic, hematoma, stoma-related complication, incontinence; radiotherapy: skin desquamation, dysuria, dehydration, weight loss, neurotoxicity; chemotherapy: febrile neutropenia, neutropenic sepsis, mucositis; targeted therapy: skin toxicity). Full details of definitions may be found in the online reference guide available at www.ichom.org/medical-conditions/colorectal-cancer

[c] Self care activities of daily living (ADL) refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

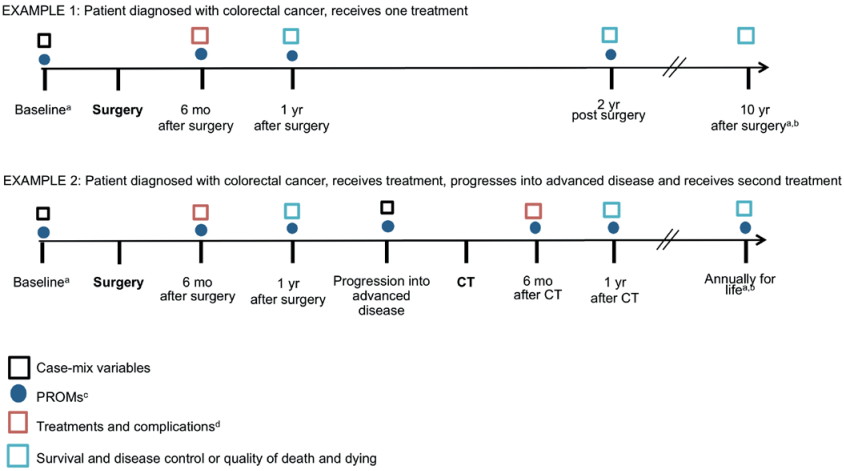

Figure 1. Sample timelines showing when outcomes and baseline factors should be collected for patients with colorectal cancer. These timelines are intended to represent the outcome data collection points for possible treatment paths a patient could take and do not advocate a particular treatment approach. Most baseline factors should be collected at the time of initiation of the colorectal cancer standard set, although several

(eg, pathological stage) are collected after treatment.

CT = chemotherapy; PROMs = patient-reported outcomes measurements.

[a]At first physician visit.

[b]Distinction for long-term follow-up: patients with local disease should receive follow-up for up to 10 years, and patients with advanced disease should receive follow-up annually for life.

[c]All PROMs will be collected at baseline, 6 months after treatment, and then annually.

[d]Collection of short-term complications is recommended when the patient is undergoing treatment or within 90 days after initiation of treatment.

Survival and Disease Control

The following measures were included for survival and disease control: overall survival, disease-specific survival, recurrence, and progression-free survival. For patients with rectal cancer receiving neo-adjuvant therapy or surgery, pathological complete response and margin status, respectively, were included because they may serve as intermediary outcomes, proxies of survival, and short-term indicators of surgical quality [21]. The recommended time frame for col-lection of data was 1 year after treatment and, if possible, annually up to 10 years.

Disutility of Care

Care disutility measures focused on short-term complications of treatment, including type and severity. An algorithm to determine severity was developed based on the grading systems of the Clavien-Dindo classification for surgical complications[22] and the Common Terminology Criteria for Adverse Events, version 4.0 for radiation therapy and chemotherapy [23].

Degree of Health (QOL, Functioning, and Symptoms)

The final QOL, functioning, and symptoms measures are listed in Table 1. Although social functioning, dietary restrictions, and vaginal symptoms were excluded after the second Delphi round (eTable 2), they were reconsidered in the final voting because of their high rating of importance by focus group patients, on the patient validation survey, and by the WG.

PROMs were used to assess the degree of health outcomes. After relevant outcomes were selected, corresponding reliable and valid measurement tools were reviewed (eTables 7 and 8). PROM tools were researched based on the outcome cover-age, psychometric quality, clinical interpretability, and feasibility to assess and implement the PROMs in daily practice. After extensive evaluation and discussion, the WG recommended the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life C30 tool [24] to capture overall QOL and the EORTC Quality of Life CR29 tool [25] to capture CRC-specific outcomes. To capture outcomes not directly assessed in the EORTC measurement tools, the Memorial Sloan Kettering Cancer Center Bowel Function dietary subscale [26] and a single item of the EORTC Quality of Life LM21 tool [27] were selected to assess dietary issues and neuropathy, respectively, for patients who received chemotherapy. All PROMs were

recommended for collection at baseline, 6 months and 1 year after treatment, and annually up to 10 years, if possible. The use of recommended PROMs is encouraged at more frequent time points during the treatment process to support communication and clinical decision-making.

Quality of Death

Several reports have outlined outcomes related to the quality of end-of-life (EOL) care [28,29]. Because research suggests that EOL hospitalization may be preventable and may indicate poor quality of care [28], the WG decided to include the outcome of more than 1 hospital ad-mission in the last 30 days of life for patients with advanced dis-ease. Place of death was included, with response options that are internationally comparable and easy to obtain [30]. The patient's preference for place of death was also included because patients often have individualized EOL care preferences and needs that necessitate assessment and documentation [29]. A measure on hospice use was included given evidence showing its benefit at the EOL, in part due to providing less aggressive care [28]. We recommend re-viewing the records of deceased patients on an annual basis for EOL outcomes.

Case-Mix Variables

Case-mix variables were included for baseline collection to allow for cross-treatment and cross-center comparison (Table 2). These variables included demographic factors, baseline clinical factors, and baseline tumor factors.

Demographic factors included age, sex, race/ethnicity, educational level, and relationship status. Because racial/ethnic disparities have been demonstrated in CRC treatment and outcomes [31], the WG determined that race/ethnicity was also important to include. However, because there is no standardized method to assess racial/ ethnic subgroups internationally, we recommend using national or regional classification systems instead. While socioeconomic status is predictive of health outcomes in patients with CRC [32], it is difficult to accurately assess. Educational level, defined as the highest level of schooling attained, is reported to serve as a good surrogate for socioeconomic status and is easily obtainable and internationally comparable [33]. Relationship status was included because it is considered to be an important aspect of social support, which is independently associated with survival [34].

Baseline clinical factors prioritized for inclusion were Eastern Cooperative Oncology Group performance status, comorbidities, cognitive status, and disorders with predisposed CRC risk. The patient-reported, modified Self-Administered Comorbidity Questionnaire [35] was selected for comorbidity reporting because it has been shown to predict functional outcomes equally as well as the Charlson Comorbidity Index [36]. Several baseline tumor factors were included, such as tumor location, clinical and pathological TNM stage, and treatment intent (Table 2). If there is more than 1 primary tumor, tumor factors of the tumor with the highest clinical TNM stage should be collected. Urgency of procedure was also included according to the United Kingdom's National Confidential Enquiry Into Peri-operative Deaths classification [37].

Treatment Variables

To provide a standardized terminology of treatment options among heterogeneous health care delivery institutions, the most commonly used treatment types in daily practice were included for local and systemic therapy, with free-text options for other treatment delivered. These variables are listed in Table 2.

Reference Guide

A reference guide, which includes sample questionnaires and time-lines, is freely available on the ICHOM website (http://www.ichom.org/medical-conditions/colorectal-cancer). The website also contains a data dictionary for all variables in the standard set.

External Input

A total of 28 health care professionals from different specialties participated in an open review period and shared feedback via an on-line survey. The respondents were confident (mean score, 6.8 on a 9-point Likert-type scale) about the comprehensiveness of the standard set and the feasibility of data collection in clinical practice (eTable 9). Main concerns raised were related to the duration of follow-up and the number of PROMs questions and data items, which could influence feasibility. One additional case-mix variable related to the tumor distance from the anal verge was included based on the feedback survey.

Table 2 – Summary of case-mix factors and treatment approaches for the ICHOM Colorectal Cancer Standard Set

Patient Population	Measure	Details	Data Sources[a]
Demographic Factors			
All patients	Date of birth	N/A	Patient-reported sources
	Gender		
	Body mass index	Height and weight	Clinical abstraction
	Ethnicity	Determined by country	Patient-reported sources
	Educational level	Level of schooling completed according to ISCED[b]	
	Relationship status	Relationship status	
Baseline Clinical Factors			
All patients	Performance status	ECOG/WHO scale for performance status	Clinical abstraction
	Comorbidities	Modified SCQ[c]	Patient-reported sources
	Cognitive status	Evidence of cognitive disorder	Clinical abstraction
	Familial Adenomatosis Polyposis	Presence of APC mutation	
	Lynch Syndrome/ Hereditary Nonpolyposis Colon Cancer	Presence of MMR or EPCAM mutation	
	Inflammatory Bowel Disease (IBD)	Clinical documentation of IBD diagnosis	
Baseline Tumor Factors			
All patients	Date of diagnosis	Initial date of histological diagnosis	Clinical abstraction
	Synchronous primary tumor	Presence of more than one primary tumor[d]	
	Tumor location	N/A	
	Clinical stage	Clinical stage per AJCC 5th - 7th	

Table 2 – Summary of case-mix factors and treatment approaches for the ICHOM Colorectal Cancer Standard Set (*continued*)

Patient Population	Measure	Details	Data Sources[a]
Patients with rectal cancer receiving surgery/RTx	Location of rectum tumor	Distance from anal verge (in mm)	
Patients with surgery/ biopsy	Tumor grade	Histological grade of tumor	
	BRAF status	Presence of BRAF mutation	
	RAS status	Presence of RAS mutation	
	MSI/DNA mismatch repair	Presence of microsatellite instability (MSI) mutation	
Patients with surgery	Pathological stage	Pathological stage per AJCC 5th - 7th	
	Number of lymph nodes resected	N/A	
	Number of lymph nodes involved		
	Lymphovascular invasion of tumor	Presence of lymphovascular invasion of tumor	
	Perineural invasion of tumor	Presence of perineural invasion in resected tumor	
	Completeness of surgical resection	Presence of residual disease after surgery according to TNM	
Baseline Treatment Factors			
Patients with surgery	Urgency of procedure	According to CEPOD score[e]	Clinical abstraction
All patients	Perforation	Presence of perforation of the bowel at site of the tumor	
	Treatment intent	Curative or palliative treatment intent	
Treatment approaches			
All patients	Surgery	Type and method of surgical procedure	Clinical abstraction
	Radiotherapy	Type of radiotherapy	
	Chemotherapy	Type of chemotherapy	
	Targeted therapy	Type of targeted therapy	
	No treatment	N/A	

N/A= not applicable; ISCED= International Standard Classification of Education; ECOG= Eastern Cooperative Oncology Group; WHO= World Health Organization; SCQ= Self-administered Comorbidity Questionnaire; RTx= radiotherapy; IBD= inflammatory bowel disease; AJCC= American Joint Committee on Cancer; APC= Adenomatous polyposis coli; MMR= mismatch repair; EPCAM= Epithelial cell adhesion molecule; TNM= Tumor, Node, Metastasis Staging System; CEPOD= Confidential Enquiry into Perioperative Deaths

[a] The data source reflects the way outcomes are collected and was determined as clinical (e.g. physician report), patient-reported (e.g. EORTC QLQ C-30) or administrative (with a combination of ways in some cases).

[b] Level of schooling defined in each country according to the International Standard Classification of Education.

[c] Have you ever been told by a doctor that you have any of the following? I have no other disease, heart disease (eg, angina, heart attack, or heart failure), high blood pressure, leg pain when walking due to poor circulation, lung disease (eg, asthma, chronic bronchitis, or emphysema), diabetes, kidney disease, liver disease, problems caused by stroke, disease of the nervous system (eg, Parkinson's disease or multiple sclerosis), other cancer (within the last 5 yr), depression, arthritis (select all that apply).

[d] If yes, please collect information of the tumor with the highest TNM stage

[e] Elective: operating room at time that suit both surgeon and patient, scheduled: operating room <3wks, early surgery preferred, not life saving, urgent: operating room <24hrs, a.s.a.p. after resuscitation, Emergency: operating room <2hrs, immediate operating room, resuscitation simultaneous with operating room

DISCUSSION

An international, multidisciplinary WG convened during 8 months to develop a standardized and comprehensive patient-centered outcomes measurement set for patients with CRC. Through the use of extensive patient input, a literature review, and expert consensus, the WG defined a final standard set, which we propose will facilitate institutions and practices in adapting to a restructuring of health care delivery and reimbursement that focuses on value (outcomes relative to cost).

We recognize that this standard set is not inclusive of all out-comes that may matter to patients. To balance the aims of the WG with the development of a product that would be practical to implement in clinical practice, the WG sought to construct a parsimonious data set. Centers are encouraged to collect additional information outside of the standard set, if desired. ICHOM has appointed a steering committee, composed of members of this working group, to convene annually and update the

standard set based on feed-back from implementers and other developments in the field of CRC treatment.

The standard set is limited by its integration of multiple PROMs. While most of the PROMs (59 of 64 [92.2%]) are from 2 well-tested instruments (EORTC Quality of Life C30 and CR29), the use of a single question from the EORTC Quality of Life LM21 and the addition of a module from the Memorial Sloan Kettering Cancer Center Bowel Function dietary subscale have not been tested in this context. These additional questions were added to inform outcomes that were prioritized by patients but not collected within the EORTC measurement system. Each recommended instrument or question has been individually validated, but further work is required to understand how to interpret these instruments within a single set of outcomes. The WG recognizes that 64 total questions represent a significant respondent burden; however, there is evidence that questions of strong salience to patients that are integrated into the clinical inter-action can outweigh increased respondent burden [38]. Experience collecting these outcomes in practice will inform whether any of these domains can be eliminated while retaining the standard set's usefulness. We anticipate that respondent burden will also be reduced through future development of item banks and computer-adaptive testing, which allow for modular selection of outcome do-mains and more precise measurement within a given domain [39].

We recognize that this recommendation will stretch the capabilities of most institutions. Routine collection of patient-reported outcomes is rare in most organizations, and much of the recommended clinical data are unstructured, making it difficult to extract for analysis. There are larger trends actively changing these capabilities. Major electronic medical record vendors and many third-party tools exist to support patient-reported data collection and integration into the electronic medical record [40,41]. These same vendors are also creating structured data fields within specialty-specific templates [42]. These changes are being driven by demands from payers and government for structured, standardized data elements to facilitate reporting of outcomes directly or through quality registries.

Collection of this data set could also be limited by the existing national infrastructure for following up patients. In some countries, through linkages made possible by national patient identifiers [43], cancer recurrence can be tracked over time. In other countries, this data collection is not possible, and in the absence of resources for manual tracking, follow-up will likely be limited to those patients who remain longitudinally at their initial treating institution.

In light of these challenges, we recommend that institutions take a stepwise approach to implementation (Figure 2), beginning with patient-reported outcomes. Evidence suggests that the use of patient-reported outcomes in cancer treatment can improve patient-physician communication, QOL, and survival while reducing emergency department visits and hospitalizations [44,45]. Incorporating patient-reported outcomes into clinical practice is also typically simpler than collecting structured clinical data, which requires specially trained medical record abstractors or redesign of clinical workflows. However, clinical data are necessary for quality improvement or value-based payment applications.

Alongside improvements in technical infrastructure, successful implementation of the standard set will require a significant change in clinical attitudes and workflow [46], starting with the desire to incorporate the patients' perspective more systemati-

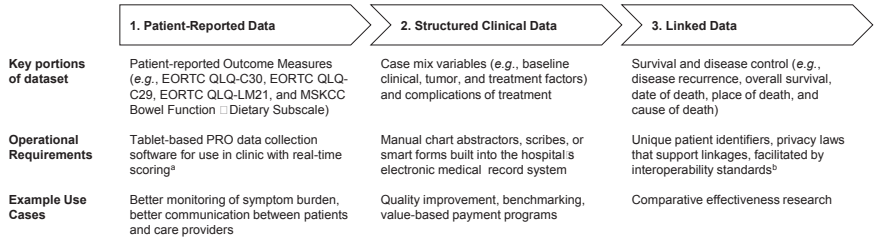

Figure 2. Sample institutional implementation plan for the colorectal cancer standard set
EORTC = European Organisation for Research and Treatment of Cancer;
MSKCC = Memorial Sloan Kettering Cancer Center; PROMs = patient-reported outcomes measurements.
[a]Increasingly available in standard electronic medical record systems.
[b]Linkage capabilities are often constrained by national health information technology infrastructure and patient privacy policies; in their absence, institutions are encouraged to follow up patients according to their best ability and resources.

cally into the care process. To help guide organizations through this process, ICHOM has developed a framework that comprises 4 phases (eFigure 2). It was designed to engage the organization and enable change as well as sustain and build on results. This framework has been successfully used across a range of conditions and settings. ICHOM's near-term implementation goal for this standard set is to partner with select members of the WG to implement the set as a proof of concept, to inform revision by the steering commit-tee, and to pave the way for broader adoption and endorsement by national policy and regulatory bodies. This approach has been successfully used for the localized prostate cancer standard set, facilitated by the Movember Foundation [47].

The goal of this project was to develop a standardized set of patient-centered outcome measures to inform value-based health care efforts in CRC care. This article describes the process by which a novel comprehensive standard set was developed to meet this need.

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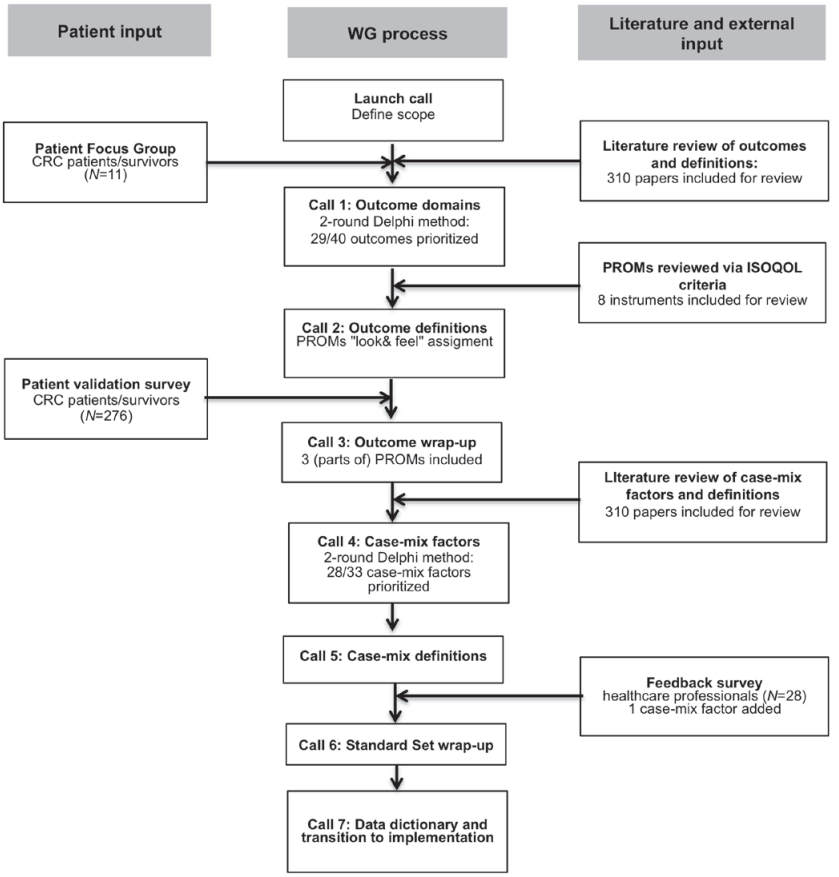
APPENDICES



eFigure 1. Summary of the development of the ICHOM Colorectal Cancer Standard Set. WG = Working Group, CRC = colorectal cancer, PROMs = patient-reported outcome measurements, ISOQOL = International Society for Quality of Life Research

eTable 1. Search Strategy Overall

Search terms		Results
#1	(((((((("Colorectal Neoplasms"[Mesh]) AND ("Quality of Life"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Outcome and Process Assessment (Health Care)" OR "Quality Indicators, Health Care"[Mesh])) NOT (("Animals"[Mesh] NOT "Humans"[Mesh]))) NOT ((Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp] OR News[ptyp] OR Case Reports[ptyp]))) AND English[Language]) AND ("06/03/2005"[Date - Publication] : "3000"[Date - Publication])) AND medline[sb])) OR (((((((((colon[tw] OR rectal[tw] OR colorectal[tw] OR rectum[tw]))) AND ((quality of life[tw] OR outcome*[tw] OR patient reported[tw] OR metric*[tw] OR measure*[tw] OR indicator*[tw]))) AND ((cancer*[tw] OR neoplas*[tw] OR carcinom*[tw] OR tumor*[tw] OR tumour*[tw] OR malignan*[tw]))) NOT ((Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp] OR News[ptyp] OR Case Reports[ptyp]))) AND ("2005/06/03"[Date - Publication] : "3000"[Date - Publication])) AND English[Language]) NOT medline[sb]) AND *article type limited to "randomized clinical trials" OR "guidelines*	1042
#2	Remove studies not meeting criteria (732 excluded in total), based on following in- and exclusion criteria: • Inclusion criteria: Randomized control trials or guidelines assessing quality of life and clinical outcomes among a general colorectal cancer patient population or colorectal cancer patients in survivorship phase OR studies assessing the validity of outcome measurement tools in colorectal cancer in randomized control trials or guidelines; studies of outcomes of population treated with usual systemic, surgical, intervention (eg stent), radiation therapy and patients with specific disease characteristics (eg metastatic, left sided cancer) that are broad classifications. • Exclusion criteria: Studies focusing on colorectal cancer patients with specified co-morbidity (ie. obesity, DM, HTN, other) or demographic group; studies focusing on the outcomes based on specific disease characteristics (eg liver metastases, tumor biology including genetic markers) or based on imaging studies; studies that evaluate specific interventions (compare one intervention to another or study interventions that are not part of usual care) or patient behaviors and their impact on quality of life or clinical outcomes; studies that are not geographically generalizable (eg done in one US state); disparities, screening studies, interventions that are educational/health services research; study protocols	310

eTable 2. Voting percentages of modified Delphi method by working group members on outcomes

		2-round Delphi % rating "very important" (7-9)		Final voting % voted "yes"			
Outcomes	Patient subgroup	Round 1 15/24	Round 2 17/24	Round 3 20/24	Round 4 20/24	Inclusion in St Set?	Comments during final voting
Survival and Disease Control							
Overall survival	All	100%				Yes	
Recurrence free survival	Curative intent	93%				Yes	
Cause-specific survival	All	87%				Yes	
Progression-free survival	Advanced disease	67%	59%	75%		Yes	It can be assessed on a shorter term than OS.
Pathologic or clinical complete response	Rectal cancer, neo-adjuvant Tx	60%	59%	70%		Yes	It may serve as an intermediary outcome and short-term indicator of surgical quality.
Margin status	Rectal cancer, surgery	60%	65%	85%		Yes	It may serve as an intermediary outcome and short-term indicator of surgical quality.
Degree of Health - Quality of Life and Functioning							
Pain/discomfort	All	93%				Yes	
Physical functioning	All	87%				Yes	
Emotional functioning	All	87%				Yes	
Overall quality of life	All	80%				Yes	
Mobility	All	80%				Yes	
Performance status	All	80%				No	Decided to include as a case-mix factor.

eTable 2. Voting percentages of modified Delphi method by working group members on outcomes (*continued*)

		2-round Delphi % rating "very important" (7-9)		Final voting % voted "yes"			
Outcomes	Patient subgroup	Round 1 15/24	Round 2 17/24	Round 3 20/24	Round 4 20/24	Inclusion in St Set?	Comments during final voting
Depression	All	73%				Yes	
Sexual functioning	All	73%				Yes	
Social functioning	All	67%	59%	65%	80%	Yes	Brought up frequently by patients of WG and FG.
Ostomy functioning	Patients with ostomy	53%	53%	85%		Yes	No main comments were made.
Cognitive functioning	All	60%	47%	60%	65%	No	Brought up frequently by patients of WG and FG. However, it was decided to include as case-mix factor.
Body image	All	53%	12%			No	
Confidence in decision making	All	53%	24%	55%		No	Brought up frequently by patients of WG/FG and survey respondents. However, it was considered too ambiguous and more related to the care experience.
Fear of ostomy	All	40%	24%			No	
Degree of Health - Symptoms							
Fatigue	All	93%				Yes	
Fecal leakage	Surgery/RTx	87%				Yes	
Erectile dysfunction	Surgery/RTx	87%				Yes	
Stool frequency	Surgery/RTx	80%				Yes	

eTable 2. Voting percentages of modified Delphi method by working group members on outcomes (*continued*)

		2-round Delphi % rating "very important" (7-9)		Final voting % voted "yes"			
Outcomes	Patient subgroup	Round 1 15/24	Round 2 17/24	Round 3 20/24	Round 4 20/24	Inclusion in St Set?	Comments during final voting
Diarrhea	Surgery/RTx	80%				Yes	
Neuropathy	CT	73%				Yes	
Gastrointestinal symptoms	Surgery/RTx	67%	71%			Yes	
Bowel function	Surgery/RTx	67%	82%			Yes	
Vaginal symptoms	Surgery/RTx	67%	53%	85%		Yes	Brought up frequently by patients of WG and FG.
Dietary restrictions	Surgery	47%	35%	70%		Yes	Brought up frequently by patients of WG/ FG and respondents of patient survey.
Ability to eat/appetite loss	All	67%	59%	50%		No	Mostly temporary.
Insomnia	All	60%	53%	40%		No	Brought up frequently by patients of WG and FG. However, it was considered to be too multifactorial and disease specific.
Weight loss	All	60%	53%	60%		No	No main comments were made.
Nausea and vomiting	All	53%	53%	55%		No	Mostly temporary.
Constipation	Surgery/RTx	53%	24%			No	
Incisional hernias	Surgery	33%	24%			No	
Skeletal events	Advanced disease	20%	24%			No	
Disutility of care							

eTable 2. Voting percentages of modified Delphi method by working group members on outcomes (*continued*)

		2-round Delphi % rating "very important" (7-9)		Final voting % voted "yes"			
Outcomes	Patient subgroup	Round 1 15/24	Round 2 17/24	Round 3 20/24	Round 4 20/24	Inclusion in St Set?	Comments during final voting
Major acute complications due to:						Yes	
Radiotherapy	RTx			67%		Yes	
Surgery	Surgery			87%		Yes	
Targeted therapy	Targeted therapy			33%		Yes	Included to capture all treatment-related morbidity.
Chemotherapy	CT			73%		Yes	
Other							
Place of death	Advanced disease	53%	33%	85%		Yes	To assess whether patient died according to patient wishes when combined with "preference for place of death".
Time spent in hospital at end of life	Advanced disease	68%	48%			No	
New suggestions after Delphi rounds							
Preference for place of death	Advanced disease			70%		Yes	
Hospital admission in last 30 days of life	Advanced disease			85%		Yes	Hospitalization at EOL may indicate poor quality of care.

eTable 2. Voting percentages of modified Delphi method by working group members on outcomes (*continued*)

		2-round Delphi % rating "very important" (7-9)		Final voting % voted "yes"			
Outcomes	Patient subgroup	Round 1 15/24	Round 2 17/24	Round 3 20/24	Round 4 20/24	Inclusion in St Set?	Comments during final voting
Time spent in acute hospital/ hospice/ home care at EOL	Advanced disease			65%		No	Too detailed for minimum dataset
Hospice care at time of death	Advanced disease				85%	Yes	

During the 2-round Delphi process, outcomes ranked as very important (score of 7-9 on 9-point Likert scale) by at least 70% in either round were included in, outcomes ranked as very important by at least 50-70% in the last voting round were voted again in the final vote and all outcomes ranked as very important by less than 50% in the last round were excluded. During the final vote, for a domain to be voted for inclusion, at least 70% had to be voted "yes".

Abbreviations: St Set = Standard Set, OS = overall survival, Tx= Therapy, WG = Working Group, FG = Focus Group, CT = Chemotherapy, RTx = radiotherapy, EOL= end of life

eTable 3. Voting percentages of modified Delphi method by working group members on case-mix factors.

		2-round Delphi % rating "very important" (7-9)		Final voting % voted "yes"		
Case-mix factor	Patient subgroup	Round 1 16/24	Round 2 19/24	Round 3 19/24	Inclusion in St Set?	Comments during final voting
Demographic factors						
Ethnicity/race	All	81%			Yes	
BMI	All	81%			Yes	
Lynch syndrome/HNPCC	All	81%			Yes	
Cognitive status	All	81%			Yes	
Date of birth	All	75%			Yes	
IBD	All	75%			Yes	
Educational level	All	69%	53%	84%	Yes	It was considered to be a good surrogate for SES, easy to obtain and internationally comparable.
FAP	All	63%	68%	84%	Yes	The WG felt it was important to collect disorders predisposing CRC
Relationship status	All	63%	58%	84%	Yes	Social support has been shown to be associated with survival.
Living status	All	69%	42%		No	
Residence (zip code)	All	69%	21%		No	
Birthplace	All	44%	26%	58%	No	
Clinical factors						
Comorbidity	All	88%			Yes	

eTable 3. Voting percentages of modified Delphi method by working group members on case-mix factors. (*continued*)

		2-round Delphi % rating "very important" (7-9)		Final voting % voted "yes"		
Case-mix factor	Patient subgroup	Round 1 16/24	Round 2 19/24	Round 3 19/24	Inclusion in St Set?	Comments during final voting
ECOG performance score	All	81%			Yes	
ASA classification	Surgery	50%	47%		No	
Tumor factors						
Pathological TNM stage	Surgery	100%			Yes	
Number of positive lymph nodes	Surgery	100%			Yes	
Number of resected lymph nodes	Surgery	100%			Yes	
Tumor location	All	94%			Yes	
Lymphovascular invasion of tumor	Surgery	94%			Yes	
Date of first histological diagnosis	All	88%			Yes	
Clinical TNM stage	All	88%			Yes	
Histological grade	Surgery/biopsy	88%			Yes	
MSI/DNA mismatch repair	Surgery/biopsy	88%			Yes	
Venous invasion of the tumor	Surgery	81%			Yes	
Perineural invasion of the tumor	Surgery	81%			Yes	
Multifocal metastatic disease	Surgery	81%			Yes	
Oligometastatic to the liver	All	81%			Yes	
BRAF status	Surgery/biopsy	75%			Yes	
KRAS status	Surgery/biopsy	75%			Yes	

eTable 3. Voting percentages of modified Delphi method by working group members on case-mix factors. (*continued*)

		2-round Delphi % rating "very important" (7-9)		Final voting % voted "yes"		
Case-mix factor	Patient subgroup	Round 1 16/24	Round 2 19/24	Round 3 19/24	Inclusion in St Set?	Comments during final voting
Obstruction at diagnosis	All	63%	63%	53%	No	
Diagnosis by screening	All	50%	47%		No	
New suggestion after Delphi:						
Perforation	All			89%	Yes	
Treatment factors						
Urgency of procedure	Surgery	88%			Yes	

During the 2-round Delphi process, factors ranked as very important (score of 7-9 on 9-point Likert scale) by at least 70% in either round were included in, factors ranked as very important by at least 50-70% in the last voting round were voted again in the final vote and all outcomes ranked as very important by less than 50% in the last round were excluded. During the final vote, for a factor to be voted for inclusion, at least 70% had to be voted "yes".
Abbreviations: St Set = Standard Set, IBD = Inflammatory Bowel Disease, HNPCC = Hereditary Nonpolyposis Colon Cancer, FAP = Familial Adenomatosis Polyposis, SES = socio-economic status, CRC= colorectal cancer, BMI = body mass index, ECOG = Eastern Cooperative Oncology Group, ASA = American Society of Anesthesiologists

eTable 4. Description of colorectal cancer patients and survivors participating in the patient survey

	Survey respondents *N* = 276
Baseline characteristics	N (%)
Age, years	
=/< 35 years	19 (7)
36 - 55 years	132 (48)
56 - 75 years	116 (42)
=/> 76 years	6 (2)
Gender	
Female	207 (75)
Male	66 (24)
Continent	
North America	146 (53)
Australia	121 (44)
Europe	8 (3)
Colon cancer	166 (60)
Locoregional	99 (36)
Metastatic	66 (24)
Rectal cancer	108 (39)
Locoregional	83 (30)
Metastatic	25 (9)
Treatment characteristics	
Diagnosis	
< 2 years ago	99 (36)
2-10 years ago	155 (56)
> 10 years ago	19 (7)
Currently on treatment	
Yes	86 (31)
No	190 (69)
Treatment	
Resection	243 (88)
Chemotherapy	44 (16)
Radiotherapy	94 (34)
Chemoradiotherapy	33 (12)
Targeted therapy	44 (16)
No treatment	8 (3)
Other	19 (7)
Stoma	
No stoma	146 (53)
Yes, reversed stoma	97 (35)
Yes, permanent stoma	30 (11)

eTable 5. Results of item scores by colorectal cancer patients and survivors participating in the patient survey.

Outcomes	% rating "very important" (score 7-9)	Mean score
Survival and Disease Control		
Overall survival	97%	8.9
Progression-free survival	97%	8.8
Recurrence free survival[d]	94%	8.7
Quality of Life and Functioning		
Physical functioning	91%	8.2
Bowel functioning	91%	8.2
Overall quality of life	88%	8.2
Mobility	84%	7.9
Ostomy functioning	80%	7.7
Emotional functioning	79%	7.7
Depression	68%	7.0
Sexual functioning	55%	6.3
Long-term side effects		
Neuropathy	64%	6.8
Fecal leakage	64%	6.7
Stool frequency	57%	6.6
Diarrhea	55%	6.4
Fatigue	54%	6.5
GI symptoms	52%	6.4
Pain	51%	6.4
Vaginal symptoms	40%	5.4
Erectile dysfunction	30%	4.6
Other		
Acute complications	72%	7.3

All outcomes were provided with supporting definitions and categorized into three types to make it more understandable for patients: 1) positive gains from treatment (e.g. reducing the risk of recurrence), corresponds with the tier survival and cancer control 2) negative impact from treatment (e.g. pain), corresponds with the tier degree of health - long-term side-effects and 3) impact on quality of life and other issues related to treatment (e.g. sexual functioning), corresponds with the tier degree of health - quality of life and functioning and the tier disutility of care

eTable 6. Additional outcomes reported by colorectal cancer patients and survivors participating in the patient survey.

Additional outcomes	No of respondents[a]:
No additional outcomes needed	229
Additional outcomes:	47
Decision-making process: Informing on QoL and side effects	15
Availability of peer groups/support teams	11
Dietary changes	9
Support for family	5
Cognitive functioning	5
Ability to work	4
Skin rashes	3
Fear of recurrence	3
Ability to eat during treatment	2
PTSD	2
Financial outcomes	2
Stress	2
GI obstruction	1
Support of doctor/sympathy	1
Information on alternative therapies	1
Retrograde ejaculation	1
One contact person	1
Fear of having ostomy	1
Worry about future	1
Body image	1
Sleeping disturbance	1
Ability to care for children	1
Fertility	1

Abbreviations: QoL = quality of life, PTSD = post-traumatic stress disorder, GI= gastro-intestinal
[a] Survey respondents could provide more than one additional outcome in the open text box

eTable 7. Overview of patient reported outcome measurements (PROMs) and their specifications for the included outcome domains.

Specifications[a]	Health-related quality-of- life (HRQOL) Instruments							
	Cancer specific QoL		Colorectal cancer specific			Colorectal cancer treatment specific		
Abbreviated name	EORTC-C30	FLIC	EORTC-CR38	EORTC-CR29	FACT-C[b]	LARS	MSKCC Bowel Function	QLICP
Conceptual framework	Med	Med	High	High	High	Med	Med	Med
Target population	Med	Med	High	High	High	Med	Med	Med
Test-retest reliability	High	Unknown	Med	Med	Unknown	Med	High	Unknown
Internal consistency	Med	Med	Med	High	High	Unknown	Unknown	Med
Content validity	High	High	High	High	High	Med	High	Med
Construct validity	high	Unknown	Med	High	High	High	Med	Unknown
Ability to detect change	high	Unknown	High	Med	High	Unknown	Med	Unknown
Interpretability	med	Med	Med	Med	Low	High	Med	High
Translation	high	High	High	High	Med	High	Low	Low
Number of items	30	22	38	29	37	5	18	23
Time to complete (min)	10	10	10	5	10	1-2	Unknown	Unknown
Administrative burden	Med	Med	Med	Med	Low	High	Med	Low
Licensing	High	Unknown	High	High	Med	Unknown	Unknown	Unknown
Locations in use	high	Low	High	High	Med	Low	Low	Low
Number of citations	High	High	High	Low	High	Med	Med	Low
Year developed	med	Low	Med	High	Med	High	High	Low

Abbreviations: EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core, FLIC = Functional Living Index for Cancer, EORTC QLQ-CR38/CR29 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer Module FACT-C =Functional Assessment of Cancer Therapy-Colorectal, LARS= Low anterior resection syndrome score, MSKCC Bowel Function= Memorial Sloan Kettering Cancer Center Bowel instrument QLCIP = Quality of Life Index for Colostomy Patients

[a] The psychometric quality of each PROM was evaluated, based on the International Society for Quality of Life Research (ISOQOL) criteria

[b] The FACT-C is an instrument which combines the FACT-General to assess cancer specific QoL and the Colorectal Cancer Subscale (CCS) to assess colorectal cancer specific QoL.

eTable 8. Overview of domain coverage of patient reported outcome measurements (PROMs)

	Health-related quality of life (HRQOL) instruments						
	Cancer specific		Colorectal cancer specific		Colorectal cancer treatment specific		
Outcomes	EORTC QLQ C30	FLIC	EORTC QLQ-C29	FACT-C[a]	LARS	MSKCC bowel function	QLICP
Overall well-being	Yes	Partially	No	Yes	No	Partially	Yes
Physical functioning	Yes	Partially	Partially	Yes	No	Partially	Partially
Emotional functioning	Yes	Partially	No	Yes	No	No	Partially
Social functioning	Yes	Partially	No	Yes	No	No	Partially
Mobility	Yes	Partially	No	Partially	No	No	Partially
Depression	Yes	Yes	No	Partially	No	No	Partially
Pain/discomfort	Yes	Partially	Partially	Yes	No	No	Yes
Fatigue	Yes	No	No	Partially	No	No	Partially
Sexual functioning	Partially	No	Partially	Partially	No	No	Partially
Bowel function	Partially	No	Partially	Partially	Partially	Yes	No
Ostomy functioning	No	No	Yes	Partially	No	No	No
Dietary issues	No	No	no	no	No	yes	No
Fecal leakage	No	No	Yes	Yes	Yes	Yes	No
Stool frequency	No	No	Yes	No	Yes	Yes	No
Diarrhea	Yes	No	Partially	Yes	Partially	Yes	No
GI symptoms	Partially	No	Partially	Partially	Partially	Yes	No
Erectile dysunction	No	No	Yes	No	No	No	No
Vaginal symptoms	No	No	Partially	No	No	No	No
Neuropathy	No	No	No	No	No	No	No

Yes = outcome covered by instrument

Partially = outcome partially covered by instrument

No = outcome not covered by instrument

Abbreviations: EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core, FLIC = Functional Living Index for Cancer, EORTC QLQ-CR38/CR29 = European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire - Colorectal Cancer Module FACT-C =Functional Assessment of Cancer Therapy-Colorectal, LARS= Low anterior resection syndrome score, MSKCC Bowel Function= Memorial Sloan Kettering Cancer Center Bowel instrument QLCIP = Quality of Life Index for Colostomy Patients.
Partially: PROM incompletely encompasses outcome desired.
[a] The FACT-C is an instrument which combines the FACT-General to assess cancer specific QoL and the Colorectal Cancer Subscale (CCS) to assess colorectal cancer specific QoL.

eTable 9. Results of item scores by respondents of feedback survey

Statements on Colorectal Cancer Standard Set	% rating "very confident" (score 7-9)	Mean score	Comments[a]
Part I. High level overview of Standard Set			
The Colorectal Cancer Standard Set represents a comprehensive overview of the most essential outcomes for CRC patients.	68%	7.0	
The in- and exclusion criteria cover the population sufficiently with treatment approaches that are considered standard of care.	75%	7.6	
The outcomes are sufficiently parsimonious to be collected routinely by patients and clinicians.	57%	6.4	Number of PROMs and clinical data items could lead to compliance issues in daily practice.
Time points for measurement are feasible to follow up patients.	61%	6.7	Collecting 5 year follow-up for patients without on-term problems might be sufficient and more feasible.
The case-mix factors are appropriately comprehensive to enable risk-model development for provider performance comparison.	54%	6.5	Tumor distance from anal verge is crucial for patients with rectal cancer as it can influence functional status.
I agree with the recommended tools, questions and methods.	79%[b]		

eTable 9. Results of item scores by respondents of feedback survey (*continued*)

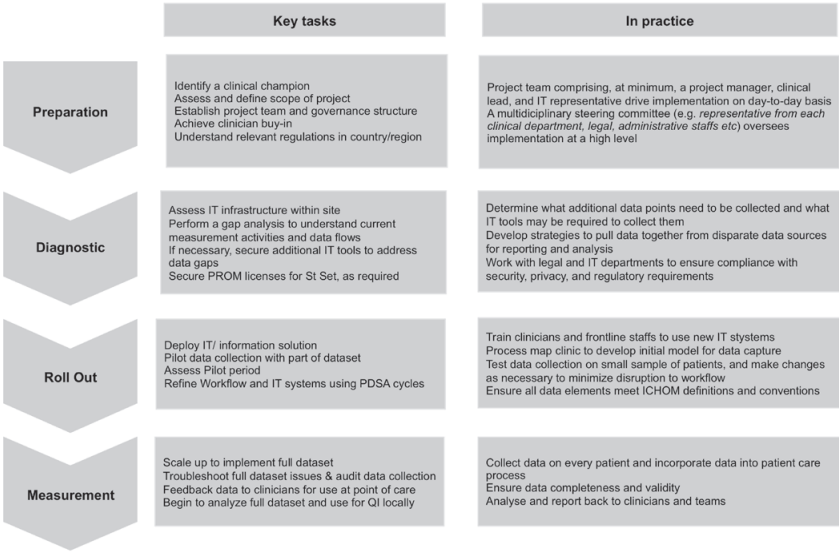
Statements on Colorectal Cancer Standard Set	% rating "very confident" (score 7-9)	Mean score	Comments[a]
Part II. Complete overview of Standard Set			
Case-mix factors are defined properly, are comprehensive enough to enable risk-adjustment and can be collected in clinical practice.	67%	7.1	
Items of patient-reported form are comprehensive enough to cover PRO domains and can be collected by patients.	63%	6.6	It could be challenging to have patients complete all PROMs
Clinical outcomes and treatment approaches are defined properly and can be collected in routine clinical practice.	67%	6.8	Collecting all items would require good IT support and linkage to the EHR system.

The online feedback survey consisted of two parts: 1) high-level overview of the Set for review of a summary of the recommended outcomes, treatment approaches, case-mix factors and in- and exclusion criteria. 2) Complete overview of the Standard Set with access to the complete Reference Guide in order to review each variable with corresponding definitions and response options. Respondents had to rate their confidence on a 9-point Likert scale (e.g. 7-9 was very confident)

[a] Total of 28 healthcare professionals completed the survey, including 10 surgeons, 5 statisticians and researchers, 4 medical oncologists, 4 gastroenterologists, 3 nurses, 2 consultants)

[b] Response option was binary ("yes/no") instead of the 9-point Likert scale

Abbreviations: CRC = colorectal cancer, IT= information technology, EHR= Electronic Health Record



eFigure 2. Phases involved in implementation of the Standard Set

7 A Standard Set of Value-Based Patient Centered Outcomes for Breast Cancer The International Consortium for Health Outcomes Measurement (ICHOM) Initiative

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JAMA Oncol 2017 May 1;3(5):677-685

ABSTRACT

A major challenge in value-based health care is the lack of standardized health outcomes measurements, hindering optimal monitoring and comparison of the quality of health care across different settings globally. The International Consortium for Health Outcomes Measurement (ICHOM) assembled a multidisciplinary international working group, comprised of 26 health care providers and patient advocates, to develop a standard set of value-based patient-centered outcomes for breast cancer (BC). The working group convened via 8 teleconferences and completed a follow-up survey after each meeting. A modified 2-round Delphi method was used to achieve consensus on the outcomes and case-mix variables to be included. Patient focus group meetings (8 early or metastatic BC patients) and online anonymized surveys of 1225 multinational BC patients and survivors were also conducted to obtain patients' input. The standard set encompasses survival and cancer control, and disutility of care (eg, acute treatment complications) outcomes, to be collected through administrative data and/or clinical records. A combination of multiple patient-reported outcomes measurement (PROM) tools is recommended to capture long-term degree of health outcomes. Selected case-mix factors were recommended to be collected at baseline. The ICHOM will endeavor to achieve wide buy-in of this set and facilitate its implementation in routine clinical practice in various settings and institutions worldwide.

INTRODUCTION

Breast cancer (BC) is the most common cancer and the most common cause of cancer death in women worldwide [1]. BC management usually requires a multimodal approach, involving surgery, radiotherapy, chemotherapy, hormonal therapy and survivorship care [2, 3]. However, there is significant variation in BC treatment across institutions, geographical regions and countries [4-9]. Multiple randomized trials have shown equivalent survivals with different BC treatments [10], hence the treatment decision often comes down to the value each patient places on the potential gains/losses associated with each treatment option.

While achieving high *value* – defined as health outcomes per dollar spent – for patients is the overarching goal of healthcare delivery [11], often, defining and measuring health outcomes can be difficult. Outcome measurements need to encompass overall disease control, treatment complications, and quality of life (QOL) during and following treatment. Recognizing the lack of consistent outcome measurements, which hampers the monitoring of routine clinical practice, as well as quality of care and outcome comparison in a systematic and meaningful manner, the International Consortium for Health Outcomes Measures (ICHOM), a nonprofit organization has initiated efforts to develop standard sets of patient-centered outcome measurements for various medical conditions such as back pain [12], coronary artery diseases [13], cataract [14] and cancers (e.g. prostate cancer [15, 16] and lung cancer [17]). Building on previous ICHOM experience and successes, an international multidisciplinary working group (WG) for BC was assembled to develop a minimal standard set of outcomes that matter most to BC patients. The set can: 1) enhance clinician-patient shared decision-making; 2) provide quality outcome information to providers and institutions to drive transparency and improvement; and 3) increase the opportunity for comparative effectiveness research.

METHODS

ICHOM breast cancer working group

The development of the set was initiated by ICHOM (www.ichom.org), (eTable 1). The WG comprised 26 experts, including clinicians (breast/plastic surgeons, medical/radiation oncologists, pathologists, radiologists and palliative care physicians), nurses, epidemiologists, patient representatives and advocacy groups, from Europe, North America, Latin America, Australia and Asia. A smaller project team (PT) (W.L.O., M.S., A.V.B., C.S., and C.S.) guided the efforts of the larger WG.

Development of breast cancer standard set

The WG convened via eight videoconferences (August 2015–April 2016), and worked through a similar process as previous ICHOM WG [15-17]. Development of the set involved several phases (Figure 1).

Development of potential outcomes and case-mix list

The PT performed a structured PubMed literature review (January 1, 2005 to July 29, 2015) (eTable 2 and eFigure 1) to identify relevant clinical and patient-reported QOL outcomes, treatment-related complications, survival measures and case-mix factors. The literature review retrieved 1360 randomized controlled trials, and a total of 398 papers were included for review. Existing BC registries were also reviewed, and WG experts were asked to identify additional relevant sources. To ensure patients' input in the outcomes selection, a focus group meeting with eight early/metastatic BC patients was conducted (guided by W.L.O., M.S. and A.V.B.), to explore patients' perspective on the importance of different outcomes, and what affected them, or other patients, the most during their day-to-day lives.

Modified 2-Round Delphi Method

After each videoconference, a survey was circulated, requiring each working group member to vote on the proposed outcomes, case-mix variables and PROMs. A modified 2-round Delphi approach (eTables 3 and 4) was used to reach consensus. In brief, the proposed outcomes or variables needed to be voted as very important (ie, score of 7-9 on a 9-point Likert scale) in either voting rounds by more than 70% of the working group members for inclusion in the set.

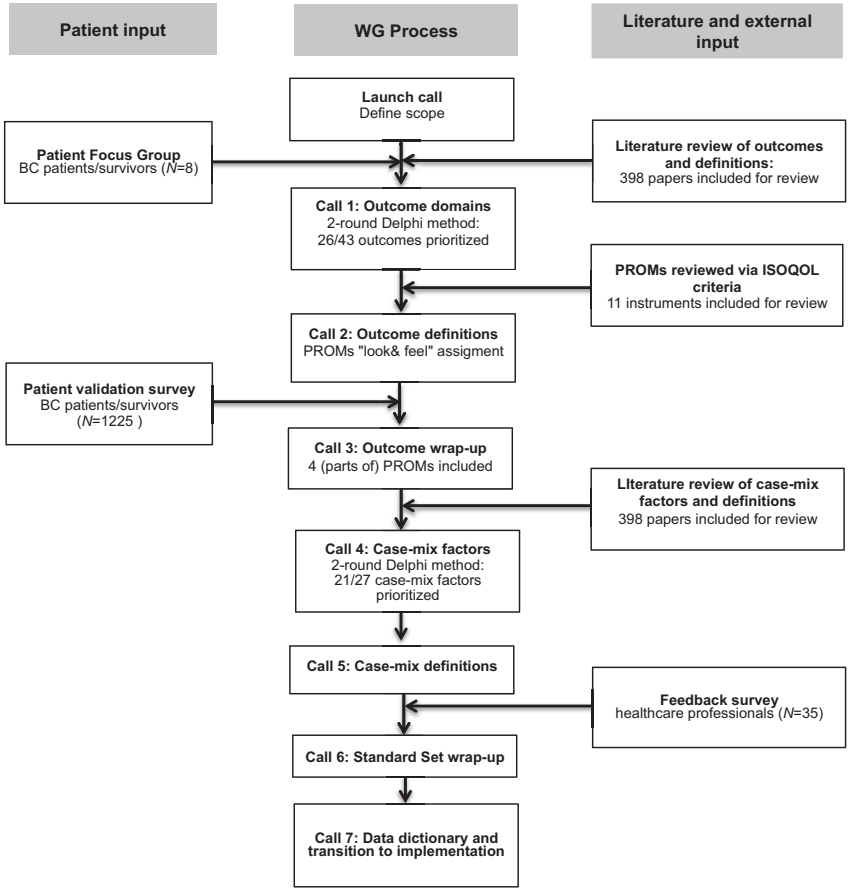

Figure 1. Summary of the development of the ICHOM Breast Cancer Standard Set
PROMs = patient-reported outcome measurements; ISOQOL = International Society for Quality of Life Research.

Outcomes Validation

The final list of outcomes was validated in 1225 multinational BC patients and survivors, recruited via several international patient organizations (eTable 5). Participants were asked to complete an anonymized survey, rating the importance of each outcome on a 9-point Likert scale, with an option of including additional outcomes in text form (eTables 6 and 7).

Selection of PROMs

After finalizing the list of outcomes, the corresponding PROMs were identified. The PROMs were evaluated by the project team, based on psychometric quality according to the International Society for Quality of Life Research (ISOQOL) criteria [18] (eTable 8) and the domain coverage (eTable 9). Prior to the voting, working group members were asked to complete the different PROMs, from a patient's perspective.

External Input

The final draft was presented to key stakeholders and others with an interest in outcome measurement for review and to provide feedback via online survey. They were asked to rate their confidence on several elements of the set (eg, completeness of the outcome list, implementation feasibility) on a 9-point Likert scale, with an open field for comments.

RESULTS

Condition and Treatment Scope

The set was designed for all pathologically confirmed American Joint Committee of Cancer (AJCC) patients with stages 0 to IV BC, including ductal carcinoma in situ (DCIS), in both men and women. Rare tumors such as Phyllodes tumors and lobular carcinoma in situ were excluded, given the difficulty in defining a standard of care for these tumor subtypes.

Outcomes

After consolidating the findings of the literature review and focus group meeting, a proposed list of 43 outcomes was identified for vote (eTable 9), the working group recommended the use of a combination of multiple PROMs (Table 1). The working group recognized that selection and recommendation of PROMs for inclusion in the set can be contentious given that there are multiple available PROMs of high psychometric quality (eg, European Organization for Research and Treatment of Cancer Quality of Life [EORTC-QLQ] and Functional Assessment of Cancer Therapy [FACT] questionnaires) that are already being used in different institutions. The PROMs were evaluated based on the outcomes cover-age, psychometric quality,

Table 1 – Summary of outcomes for the ICHOM Breast Cancer Standard Set

Patient Population	Measure		Data Sources[a]
Survival and Disease Control			
All patients	Overall survival		Administrative
	Death attributed to breast cancer		
Patients with curative intent	Recurrence free survival (local, regional or distant)		Clinical
Degree of Health			
All patients	Overall well-being	Tracked via EORTC QLQ-C30	Patient-reported
	Physical functioning		
	Emotional functioning		
	Cognitive functioning		
	Social functioning		
	Ability to work		
	Anxiety		
	Depression		
	Insomnia		
	Financial impact		
	Pain		
	Fatigue		
	Sexual functioning	Tracked via EORTC QLQ-BR23	
	Body image		
Patients with surgery/ radiotherapy	Satisfaction with breast(s)	Tracked via BREAST-Q- Satisfaction with Breasts domain	
	Arm symptoms	Tracked via EORTC QLQ-BR23	
	Breast symptoms		
Patients with systemic therapy	Vasomotor symptoms		
	Peripheral neuropathy	Tracked via EORTC QLQ-LMC21- one item	
	Vaginal symptoms	Tracked via ES of the FACT - six items	
	Arthralgia		

Table 1 – Summary of outcomes for the ICHOM Breast Cancer Standard Set (*continued*)

Patient Population	Measure	Data Sources[a]
Disutility of Care		
Patients with surgery	Reoperations due to involved margins	Clinical/patient-reported
All patients with treatment	Severity of acute complications based on the Clavien-Dindo and CTCAE	Clinical
	Name of acute complication	

EORTC QLQ= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, C= Core module BR= Breast Cancer module, LMC=Colorectal Liver Metastases, FACT =Functional Assessment of Cancer Therapy, ES= Endocrine Subscale, CTCAE= US National Cancer Institute Common Terminology Criteria for Adverse Events

[a] The data source reflects the way outcomes are collected and was determined as clinical (e.g. physician report), patient-reported (e.g. EORTC QLQ C-30) and administrative (e.g. Death registry), in some cases a combination.

clinical interpretability, and feasibility of PROMs implementation in daily practice (eTables 8 and 9). After extensive discussions and a "look-and-feel" assignment, the use of EORTC-QLQ-Core (C30) [24] and EORTC-QLQ-Breast Cancer (BR23) [25] was eventually recommended by the working group to capture the core cancer-specific and BC-specific outcomes. The working group also recommended additional questions from other PROMs to capture outcomes not encompassed by the EORTC questionnaires. These included the BREAST-Q [26] sub-scale for breast satisfaction, a single item from EORTC-QLQ-Liver Metastases (Colorectal) (LMC21) [27] for peripheral neuropathy, and 6 items from the FACT-Endocrine Subscale (ES) [28] for vaginal symptoms and arthralgia. The assessment of degree of health outcomes was recommended at baseline (ie, at diagnosis), 6 months after primary surgery, and annually thereafter (Figure 2). Follow-up was recommended up to 10 years in early BC patients to capture the period during which patients might still be on endocrine therapy.

Case-Mix Variables

The working group identified a minimal set of demographic, clinical, and tumor-related factors to be collected at baseline for meaningful outcome comparisons (Table 2). While socioeconomic status (SES) is an important demographic factor, accurate characterization of SES can be complex, involving multiple components

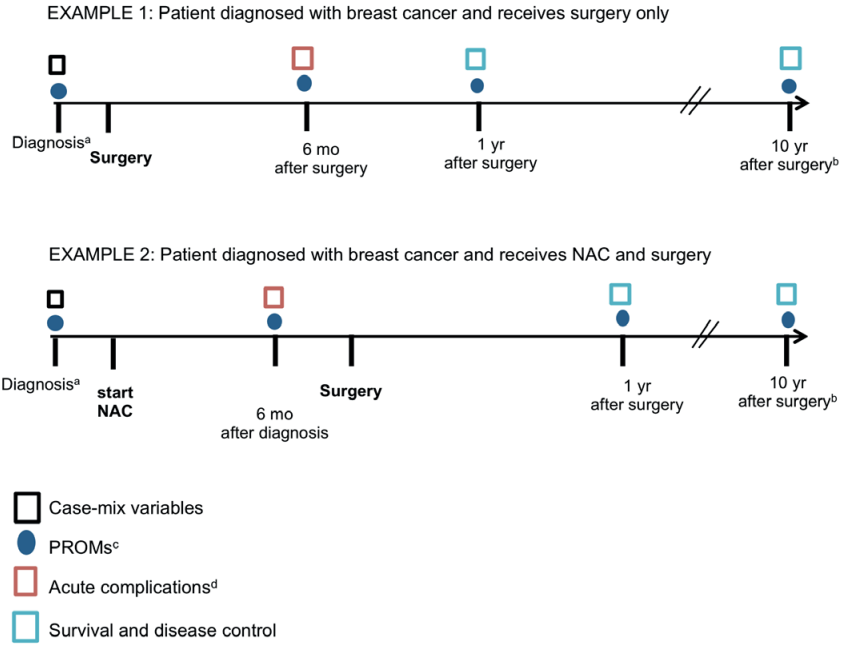

Figure 2. Sample timelines illustrating when particular outcomes and baseline factors should be collected for patients with breast cancer.

These timelines are intended to represent the outcome data collection points for possible treatment paths a patient could take, and do not advocate a particular treatment approach. Of note, a majority of baseline factors should be collected at the time of initiation of the Breast Cancer Standard Set, although several (eg, pathologic stage) are collected after treatment. NAC indicates neoadjuvant chemotherapy; PROMs, patient-reported outcome measurements.

[a]Collection of acute complications is recommended while the patient is undergoing treatment or within 90 days of treatment completion, except for complications of hormonal therapy which will be collected up to 1 year.

[b]All PROMs will be collected at baseline, 6 months after treatment, and then annually, except for the BREAST-Q-Satisfaction with Breasts domain, which will only be collected at baseline,1 year, and 2 years after treatment.

[c]Distinction for long-term follow-up: patients with local disease; follow-up up to 10 years, patients with advanced disease; follow-up annually for life

such as occupation and income. As with previous ICHOM working groups, the BC working group recommended the collection of education level based on the International Standard of Schooling Classification [29] because it is reported to be a good surrogate for SES, easy to obtain, and globally comparable [30]. Relationship

Table 2 – Summary of case-mix factors[a] and treatment approaches for the ICHOM Breast Cancer Standard Set

Patient Population	Measure	Data Sources[b]
Demographic Factors		
All patients	Gender	Patient-reported
	Date of birth	
	Body mass index	Clinical
	Ethnicity	Patient-reported
	Educational level[c]	
	Relationship status	
	Menopausal status	
Baseline Clinical Factors		
All patients	Comorbidities via the modified SCQ[d]	Patient-reported
	Laterality	Clinical
	Second primary tumor	
Baseline Tumor Factors		
All patients	Date of histological diagnosis	Clinical
	Histological type	
	Mutation status predisposing BC	
	Tumor grade (invasive)	
	Tumor grade (DCIS)	
Patients with NAC	Clinical TNM stage (AJCC 7th)	
Patients with surgery	Pathological TNM stage (AJCC 7th)	
	Size of invasive component of tumor (in mm)	
	Number of lymph nodes resected	
	Number of lymph nodes involved	
	Estrogen receptor status	
	Progesteron receptor status	
	Her-2 receptor status	
Treatment approaches		
All patients	(Reconstructive) surgery	Clinical/ patient-reported
	(Neo)adjuvant radiotherapy	
	(Neo)adjuvant chemotherapy	
	Targeted therapy	
	(Neo)adjuvant hormonal therapy	
	No therapy	

SCQ = Self-administered comorbidity questionnaire, DCIS = ductal carcinoma in situ, BC = breast cancer, NAC= neo-adjuvant therapy, AJCC = American Joint Committee on Cancer, DCIS = ductal carcinoma in situ

[a] All case-mix factors include measures with corresponding patient populations, definitions or supporting information, timing for collection and source of data.

[b] The data source reflects the way outcomes are collected and was determined as clinical (e.g. physician report), patient-reported (e.g. EORTC QLQ C-30) and administrative, in some cases a combination.

[c] Level of schooling defined in each country according to the International Standard Classification of Education.

[d] Have you ever been told by a doctor that you have any of the following? I have no other disease, heart disease (eg, angina, heart attack, or heart failure), high blood pressure, leg pain when walking due to poor circulation, lung disease (eg, asthma, chronic bronchitis, or emphysema), diabetes, kidney disease, liver disease, problems caused by stroke, disease of the nervous system (eg, Parkinson's disease or multiple sclerosis), other cancer (within the last 5 yr), depression, arthritis (select all that apply).

status is also included, because it is an indicator of available social support and is associated with survival and several functional outcomes [31]. Race and ethnicity did not meet the predefined voting criteria for inclusion in the set. However, because there is evidence suggesting its potential association with treatment decisions [32] and outcomes [33,34] for certain countries, it was decided to include this as optional.

Patients' baseline health status is another important factor influencing treatment decision-making and eventual treatment out-comes. However, the Eastern Cooperative Oncology Group (ECOG) performance status scoring is deemed to be an oversimplified representation of patients' health status, and is not commonly collected in patients with early stage BC. Likewise, collection of the Charlson Comorbidity Index (CCI) can be burdensome. Therefore, the working group recommended the use of the modified Self-administered Comorbidity Questionnaire (SCQ) to capture a list of relevant medical comorbidities [35], and baseline health status as measured by the EORTC-QLQ-C30/BR23 (Table 1). It has been shown that SCQ predicts functional outcomes as well as the CCI [36] Tumor factors to be collected are based on the AJCC TNM staging. Information on hormone and human epidermal growth factor receptor 2 status are recommended to be collected as a binary data ("yes" or "no"), recognizing variability in pathology reporting between institutions and countries.

Treatment Variables

To provide a standardized terminology of treatment options over heterogeneous, international health care settings, the most commonly used treatment modalities in daily practice were included (Table 2). Patients should also be asked to report on their ongoing treatments during follow-up because clinical data may be inaccurate, especially with endocrine therapy adherence [37].

External Input

A total of 35 health care professionals from different specialties completed the survey. The respondents were confident (mean score, 6.7 on 9-point Likert scale) of the comprehensiveness of the outcome list, case-mix variables, and feasibility of data collection in routine clinical practice (eTable 10). The main concerns raised were related to the lack of end-of-life (EOL) care outcomes, and the number of PROMs items, which could lead to noncompliance.

Data Collection and Implementation

The next crucial step after finalizing the BC set is the adoption and implementation of the set. To minimize variability and inconsistency in data collection, a reference guide including sample questionnaire s and a data dictionary has been created by ICHOM (http://www.ichom.org /medical-conditions/breast-cancer/). This will cover the potential source of the data, including clinical records and patient-reported sources, as well as frequency for each data collection.

DISCUSSION

With rising health care costs, and the options of multiple treatment modalities and prolonged survival among patients with BC, the importance of value-based health-care is increasingly being recognized [38]. However, a major challenge in value-based health care is the lack of standardization in outcome measurements meaningful to patients across different cultural and geographical settings [38]. The ICHOM has therefore convened an international multidisciplinary working group, from middle- to high-income countries, to develop a standard set of patient-centered outcomes that should be measured in all patients with BC.

The aim was to develop a set, which can, and should be collected in routine clinical practice, even in resource-limited health systems. We acknowledge that randomized controlled trials remain the gold standard for treatment outcomes comparison; however, the measurement of outcomes in routine clinical practice will better reflect outcomes in a real life setting. Furthermore, the set can function as a core outcomes measurement to be collected in trial set-tings, and can be expanded to include additional outcomes, based on individual trial requirements.

We are cognizant of the need to collect minimal data to limit bur-den to both health care providers and patients, but at the same time recognize the need to encompass important outcomes for meaningful comparisons. More than 80% of the multinational survey respondents agreed with the set, providing support that the set captures the key outcomes relevant to patients with BC. The working group is aware that the recommendation of collecting (part of) multiple PROMs, ranging from 59 to 82 questions, represents significant patient burden. However, patient representatives in the working group did not find the PROMs too cumbersome, because they are all salient questions. The EORTC is currently developing computerized adaptive testing (CAT) versions, which should reduce respondent burden [39]. In addition, there is evidence suggesting clinical benefits in symptom-monitoring with PROM during routine cancer treatment [40].

The primary PROMs recommended by the working group are based on the EORTC questionnaire. However, other PROMs, such as the FACT questionnaire, are also commonly used in many institutions. In fact there is no strong evidence to suggest that the psychometric properties of 1 PROMs are superior to the other [41]. However, the EORTC questionnaire was deemed to be less ambiguous by the working group (after having completed both EORTC and FACT questionnaires themselves), and has wider outcomes coverage, encompassing outcomes such as cognitive functioning and financial impact. The working group recognized that switching across to the EORTC questionnaire might cause disruption in longitudinal data collection in institutions not currently using it. Hence, future studies are definitely warranted in making commonly used PROMs comparable, to allow for transition into the implementation of the standardized measurement recommended by the working group.

To our knowledge, this is the first international set incorporating outcomes of almost a full cycle of BC care, from diagnosis to completion of treatment and long-term survivorship, with an emphasis on patient-reported outcomes. Other entities currently measuring BC care outcomes have largely been monodisciplinary, focusing largely on surgical treatments [42,43], are more related to measuring and de-fining quality by processes and short-term outcomes of BC care [44-46], or have been set up for a short research period [47]. It is also important to acknowledge that the BC set does not include outcomes measurement on EOL care. While EOL care was raised during several video-conferences, the working group felt that EOL care is often not BC-specific, and ICHOM will consider assembling a palliative care working group to develop a standard set encompassing EOL care across various cancers and medical conditions.

To facilitate the implementation and for practicality, the working group has developed a measurement timeline in such a way that the PROMs collection runs in conjunction with patients' follow-up visits, and so the data can be used as part of clinical consultation. Even so, ICHOM recognizes the challenges involved in implementation. Routine collection of this set in clinical settings will require investment in human resources and information technology, and will depend on the active involvement of clinicians, who must see the value of having such data at the point of care, as well as for retrospective and comparative analyses.

Initially, ICHOM aims to facilitate the implementation process in a number of pilot institutions. The experience and lessons learned from these institutions will be documented, and feedback to a steering committee comprising a subgroup of the current working group members, to refine the set and to prepare it for widespread adoption. This approach has been successfully adopted for the localized prostate cancer set, facilitated by the Movember Foundation [48]. The implementation process will involve 4 phases: (1) to engage clinical champions and establish proper governance process; (2) to identify current measurement audit practices and gaps, and suggest practical strategies for collecting structured clinical data and administrating PROM assessment at the indicated time points; (3) to use pilot sites to trial strategies including existing data sets collection; and (4) to establish how to feedback the data to the clinical teams (**eTable 12**).

CONCLUSIONS

Through the use of literature review and extensive patient input, an international multidisciplinary team of BC experts has developed a minimal standard set of value-based patient-centered outcome measures, deemed to be most important to patients with BC, and generally applicable worldwide. It is recommended that the set is collected in routine clinical practice. This will allow for monitoring and meaningful comparison of BC treatment outcomes within, and across, countries, and in the longer term facilitate improvement in BC care worldwide.

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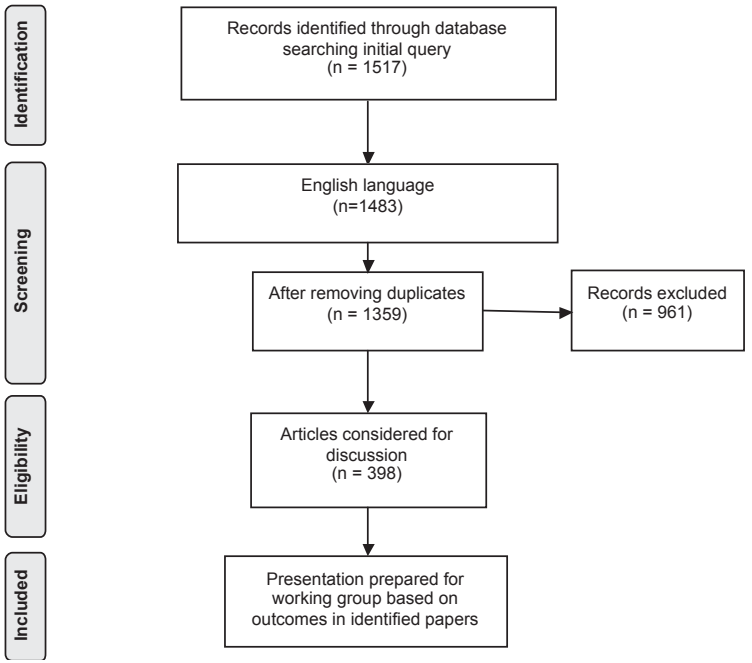
APPENDICES

eTable 1. List of contributors of the International Consortium for Health Outcomes Measurement

Hospitals and Health Systems	Patient advocacy and specialty organizations	Payors/ Governments	Founders
Alliance of Dedicated Cancer Centers	American Society for Clinical Pathology	Carl Benet AB	The Boston Consulting Group
Associacao Nacional de Hospitais Privados	American Heart Association/American Stroke Association	CZ	Institute for Strategy and Competitiveness
Boston Children's Hospital	British Heart Foundation	Harvard Pilgrim HealthCare Foundation	Karolinska Institutet
Canisius-Wilhelmina Ziekenhuis: Santeon	Bowel Cancer Australia	Government of South Australia	
Catharina Ziekenhuis: Santeon	International Urogynecological Association	NHS Camden Clinical Commissioning Group	
Connecticut Joint Replacement Institute	Macula Foundation	NHS Wales	
Erasmus University Medical Center	Macular Society	NHS England	
Generale de Sante	Movember Foundation	The Scottish Government	
Great Ormond Street Hospital	Ordem dos Enfermeiros	Dutch Institute for Clinical Auditing	
Hoag Orthopedic Institute	Oxford Academic Health Science Network		
Hoag	Retina Suisse		
Humanitas Research Hospital	NSW Agency for Clinical Innovation		
Jewish General Hospital Foundation	Wemind		
University Cancer Center Leiden The Hague	MD Anderson Physicians Network		
Martini Ziekenhuis: Santeon			
MD Anderson Cancer Center			

eTable 1. List of contributors of the International Consortium for Health Outcomes Measurement (*continued*)

Hospitals and Health Systems	Patient advocacy and specialty organizations	Payors/ Governments	Founders
Medisch Spectrum Twente: Santeon			
Onze Lieve Vrouwe Gasthuis: Santeon			
Partners Healthcare			
Providence Health&Services			
Ramsay Healthcare			
Sahlgrenska Universitetssjukhuset			
Saint Francis Care			
Save Sight Institute			
Sick Kids			
St. Antonius Ziekenhuis: Santeon			
St. Erik Eye Hospital			
Tenet Health			
Texas Children's Hospital			
The Chaim Sheba Medical Center at Tel Hashomer			
The Children's Hospital of Philadelphia			
UZ Leuven			
Uppsala University Hospital			
WillsEye Hospital			



eFigure 1. Modified PRISMA diagram

eTable 2. Search Strategy Overall

Search terms		Results
#1	"breast neoplasms"[MeSH Terms] AND ((("randomized controlled trials as topic"[MeSH Terms] OR (("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]) OR randomized controlled trial,[All Fields] OR ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trials"[All Fields] OR "randomised controlled trials"[All Fields]))) OR (("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trial"[All Fields] OR "randomized controlled trial"[All Fields]) OR ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trials"[All Fields] OR "randomized controlled trials"[All Fields]))) OR randomized controlled trial[Publication Type]) AND ((("Quality of Life"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh]) OR "Outcome and Process Assessment (Health Care)"[All Fields]) OR "Quality Indicators, Health Care"[Mesh]) AND ("2005/01/01"[PDAT] : "2015/07/31"[PDAT]) AND Clinical Trial[ptyp]	1517
#2	#1 AND English[lang]	1483
#3	Remove duplicates	1359
#4	Remove studies not meeting criteria (961 excluded in total) • 17 studies on screening or prevention of breast cancer • 13 studies on cancer imaging • 157 studies on histopathology reporting/ tumour biology/ genetic/ molecular/ biomarkers/ pharmacokinetics • 46 studies on prediction tools development • 61 studies on focusing on breast surgery/ radiotherapy techniques • 388 studies solely on lifestyle, dietary, behavioral, or other non-conventional interventions • 27 studies on cost-effectiveness study/ health services • 147 studies solely on intervention of specific treatment side effects • 105 studies outside the scope of this work (genetic counseling, study design evaluation, research methods, study protocol)	398

eTable 3. Voting percentages of modified Delphi method by working group members on outcomes

Outcomes	Patient subgroup	2-round Delphi % rating "very important" (7-9)		Final voting rounds % voted "yes""			Comments during final voting
		Round 1 19/24	Round 2 21/24	Round 3 21/24	Round 4 22/24	Inclusion in StSet?	
Survival and Disease Control							
Overall survival	All	100%				yes	
Recurrence free survival[a]	Curative intent	84%				yes	
Cause-specific survival	All	79%				yes	
Pathologic complete response	NAC	37%	24%			No	
Progression-free survival	Advanced disease	37%	29%			No	
Degree of Health - QoL and Functioning							
Physical functioning	All	95%				yes	
Emotional Functioning	All	95%				yes	
Ability to work	All	89%				yes	
Sexual functioning	All	89%				yes	
Body image	All	84%				yes	
Overall well-being	All	79%				yes	
Social functioning	All	79%				yes	
Depression	All	79%				yes	
Cognitive functioning	All	74%				yes	

eTable 3. Voting percentages of modified Delphi method by working group members on outcomes (*continued*)

Outcomes	Patient subgroup	2-round Delphi % rating "very important" (7-9)		Final voting rounds % voted "yes""			Comments during final voting
		Round 1 19/24	Round 2 21/24	Round 3 21/24	Round 4 22/24	Inclusion in StSet?	
Anxiety	All	68%	71%			yes	
Mobility	All	63%	33%			No	
Worry	All	63%	24%			No	
Confidence in decision making	All	63%	38%	67%	55%	No	Revote in final rounds brought up frequently by patients of WG/FG and survey respondents. However, it was considered too ambiguous, multifactorial and difficult to measure.
Stress	All	42%	24%			No	
Performance status	All	42%	24%			No	
New suggestions during or after 2 Delphi rounds							
Satisfaction with breast(s)	Surgery/RTx			90%		Yes	
Financial impact	All				77%	Yes	Brought up frequently in patient surveys.
Ability to fulfill household activities	All		38%			No	
Degree of Health - Long-term side-effects							
Breast symptoms	Surgery/RTx	100%				Yes	

eTable 3. Voting percentages of modified Delphi method by working group members on outcomes (*continued*)

Outcomes	Patient subgroup	2-round Delphi % rating "very important" (7-9)		Final voting rounds % voted "yes""			Comments during final voting
		Round 1 19/24	Round 2 21/24	Round 3 21/24	Round 4 22/24	Inclusion in StSet?	
Arm symptoms	Surgery/RTx	100%				Yes	
Pain/discomfort	All	89%				Yes	
Fatigue	All	84%				Yes	
Peripheral neuropathy	Systemic therapy	74%				Yes	
Arthralgia	Systemic therapy	74%				Yes	
Vasomotor symptoms	Systemic therapy	68%	52%	81%		Yes	Brought up frequently by patients of WG and FG.
Vaginal symptoms	Systemic therapy	68%	57%	81%		Yes	Brought up frequently by patients of WG and FG.
Skin fibrosis	Surgery/RTx	63%	43%			No	
Osteoporosis	Systemic therapy	63%	43%			No	
Donor site morbidity	Reconstruction	63%	57%	62%		No	Too specific for a minimum dataset.
Skeletal events	Advanced disease	63%	52%	62%		No	Too specific for a minimum dataset.
Cardiac dysfunction	Systemic therapy	58%	52%	33%		No	Too uncommon for a minimum dataset.

eTable 3. Voting percentages of modified Delphi method by working group members on outcomes (*continued*)

Outcomes	Patient subgroup	2-round Delphi % rating "very important" (7-9)		Final voting rounds % voted "yes""			Comments during final voting
		Round 1 19/24	Round 2 21/24	Round 3 21/24	Round 4 22/24	Inclusion in StSet?	
Infertility	Systemic therapy	58%	67%	67%		No	Only relevant for a relatively small subgroup.
Insomnia	All	53%	43%	70%		Yes	Brought up frequently by patients of WG and FG.
Menopausal state	Systemic therapy	53%	62%			No	
Shortness of breath	Advanced disease	53%	38%			No	
Weight disturbance	All	47%	48%			No	
Endometrial cancer	Systemic therapy	47%	24%			No	
Gastrointestinal symptoms	Systemic therapy	32%	19%			No	
Skin rash	Systemic therapy	32%	19%			No	
Hair loss	Systemic therapy	26%	24%			No	
Quality of death and dying							
Duration of time spent in hospital at end of life	Advanced disease	68%	62%			No	

eTable 3. Voting percentages of modified Delphi method by working group members on outcomes (*continued*)

Outcomes	Patient subgroup	2-round Delphi % rating "very important" (7-9)		Final voting rounds % voted "yes""			Comments during final voting
		Round 1 19/24	**Round 2** 21/24	**Round 3** 21/24	**Round 4** 22/24	**Inclusion in StSet?**	
Place of death	Advanced disease	53%	48%	43%		No	Too multifactorial, cultural and health system dependent.
New suggestion after two Delphi rounds							
Preference for place of death	Advanced disease			43%		No	Too variable between cultures, countries and patient health status.

During the 2-round delphi process, outcomes ranked as very important (score of 7-9 on 9-point Likert scale) by at least 70% in either round were included in, outcomes ranked as very important by at least 50-70% in the last voting round were voted again in the final vote and all outcomes ranked as very important by less than 50% in the last round were excluded. During the final vote, for a domain to be voted for inclusion, at least 70% had to be voted "yes".

Abbreviations: StSet = Standard Set, NAC = neoadjuvant chemotherapy, QoL = quality of life, RTx = radiotherapy, WG = Working Group, FG = Focus Group

eTable 4. Voting percentages of modified Delphi method by working group members on case-mix factors.

Case-mix domain	Patient subgroup	2-round Delphi % rating "very important"(7-9) Round 1 16/24	Round 2 19/24	Final voting rounds % voted "yes" Round 3 19/24	Inclusion in Standard Set?	Main comments during final voting
Demographic factors						
Date of birth	All	89%			Yes	
Educational level (surrogate for SES)	All	78%			Yes	
Ethnicity/race	All	67%	45%	67%	Yes	Included as optional as it has been shown to be associated with survival in several countries.
Relationship status (surrogate for social support)	All	56%	35%	81%	Yes	Included, because social support has been shown to be associated with survival.
Living status	All	56%	25%		No	
Residence (zip code)	All	50%	35%		No	
Clinical factors						
Comorbidity	All	83%			Yes	
BMI	All	83%			Yes	
Menopausal status	All	83%			Yes	
History of breast cancer	All	78%			Yes	
ECOG performance status	All	50%	40%		No	
ASA classification	All	28%	15%		No	

eTable 4. Voting percentages of modified Delphi method by working group members on case-mix factors. (*continued*)

Case-mix domain	Patient subgroup	2-round Delphi % rating "very important"(7-9) Round 1 16/24	Round 2 19/24	Final voting rounds % voted "yes" Round 3 19/24	Inclusion in Standard Set?	Main comments during final voting
New suggestion during Delphi:						
Past chest wall radiotherapy	All		40%		No	
Tumor factors						
Estrogen receptor	Surgery	94%			Yes	
Her-2 receptor	Surgery	94%			Yes	
Date of first histological diagnosis	All	89%			Yes	
Progesterone receptor	Surgery	89%			Yes	
Pathological TNM stage	Surgery	83%			Yes	
Size invasive component of tumor	Surgery	83%			Yes	
Number of positive lymph nodes	Surgery	83%			Yes	
Tumor grade	All	78%			Yes	
Second primary tumor	All	72%			Yes	
Histological type	All	72%			Yes	
mutation status	All	72%			Yes	
Multifocality	All	67%	45%		No	

eTable 4. Voting percentages of modified Delphi method by working group members on case-mix factors. (*continued*)

Case-mix domain		2-round Delphi % rating "very important"(7-9)		Final voting rounds % voted "yes"	Inclusion	Main comments during final voting
	Patient subgroup	Round 1 16/24	Round 2 19/24	Round 3 19/24	in Standard Set?	
Clinical TNM stage	All	67%	60%	76%	Yes	Included when it will only be collected for patients with NAC solely.
Number of resected lymph nodes	Surgery	61%	65%	95%	Yes	Included because it is associated with severity of lymphedema and could influence RT decisions.

During the 2-round delphi process, factors ranked as very important (score of 7-9 on 9-point Likert scale) by at least 70% in either round were included in, factors ranked as very important by at least 50-70% in the last voting round were voted again in the final vote and all outcomes ranked as very important by less than 50% in the last round were excluded. During the final vote, for a factor to be voted for inclusion, at least 70% had to be voted "yes".
Abbreviations: SES = socio-economic status, BMI = body mass index, ECOG = Eastern Cooperative Oncology Group, ASA = American Society of Anesthesiologists, NAC = neo-adjuvant chemotherapy

eTable 5. Description of breast cancer patients and survivors participating in the patient survey

	Survey respondents *N* = 1225
Baseline characteristics	N (%)
Age, years	
=/< 35 years	12 (1)
36 - 45 years	98 (8)
46 - 65 years	821 (67)
=/> 66 years	221 (18)
Continent	
North America	86 (7)
Australia	502 (41)
Europe	625 (51)
Diagnosis	
< 2 years ago	221 (18)
2-10 years ago	809 (66)
> 10 years ago	196 (16)
Disease stage	
Locoregional	1101 (90)
Metastatic	98 (8)
Treatment characteristics	
Currently on treatment	
Yes	515 (42)
No	698 (57)
Surgical treatment	
Mastectomy	662 (54)
Breast-conserving therapy	515 (42)
Breast reconstruction therapy	306 (25)
Sentinel node biopsy	698 (57)
Axillary/lymph node dissection	686 (56)
Non-surgical treatment	
Chemotherapy	784 (64)
Radiotherapy	784 (64)
Hormonal therapy	821 (67)
Targeted therapy	172 (14)
No treatment	12 (1)
Other	86 (7)

eTable 6. Results of item scores by breast cancer patients and survivors participating in the patient survey.

Outcomes	% rating "very important" (score 7-9)	Mean score
Survival and Cancer Control		
Recurrence free survival	97%	8.8
Overall survival	96%	8.8
Quality of Life and Functioning		
Emotional functioning	90%	8.0
Physical functioning	90%	8.0
Overall QoL	88%	8.1
Cognitive functioning	85%	7.8
Ability to work	83%	7.7
Social functioning	81%	7.6
Body image	64%	6.8
Sexual functioning	58%	6.6
Satisfaction with breast(s)	56%	6.4
Anxiety	45%	5.6
Depression	44%	5.4
Long-term side effects		
Fatigue	60%	6.6
Arthralgia	51%	5.9
Vasomotor symptoms	48%	5.8
Arm symptoms	47%	5.7
Peripheral neuropathy	45%	5.5
Pain	39%	5.4
Breast symptoms	36%	5.3
Vaginal symptoms	33%	4.7
Disutility of care		
Acute complications	50%	5.3

All outcomes were provided with supporting definitions and categorized into three types to make it more understandable for patients: 1) positive gains from treatment (e.g. reducing the risk of recurrence), corresponds with the tier survival and cancer control 2) negative impact from treatment (e.g. pain), corresponds with the tier degree of health - long-term side-effects and 3) impact on quality of life and other issues related to treatment (e.g. sexual functioning), corresponds with the tier degree of health - quality of life and functioning and the tier disutility of care

eTable 7. Additional outcomes reported by breast cancer patients and survivors participating in the patient survey.

Additional outcomes	**No of respondents[a]:**
No additional outcomes needed	992
Additional outcomes:	233
Decision-making process: Informing on QoL and side effects	42
Financial impact	15
Availability of peer groups/support teams	12
Fear of recurrence	10
Impact on (relationship with) family/friends	10
Acceptance of new life	10
Support/empathy from medical team	10
Hair loss	10
osteoporosis	5
Fertility	4
Support for family/children	4
Support from family/friends	4
Counseling partner/family	3
Information on alternative therapies	3
Worry about the future	3
Cardiomyopathy/cardiac toxicity	3
Weight gain	3
Genetic screening	3
Loss of confidence	2
Fear of lymphoedema	2
Spiritual well-being	2
Ability to eat	2
Insomnia/sleep disturbance	2
Able to do sport activities	2
Waiting times	1
Pulmonary embolism	1
Radiation pneumonitis	1
Balance problems	1
Sexual self-image	1
PTSD	1
Genetic screening	1
Information on nutrition	1
Nausea and vomiting	1

Abbreviations: QoL = quality of life, PTSD = post-traumatic stress disorder

[a] Survey respondents could provide more than one additional outcome in the open text box

eTable 8. Overview of patient reported outcome measurements (PROMs) and their specifications for the included outcome domains.

	Health-related quality-of- life (HRQOL) Instruments											
Specifications[a]	Cancer specific QoL			Breast cancer specific			Breast cancer treatment specific					
Abbreviated name	EORTC-C30	FACT-G	CARES-SF	EORTC-BR23	FACT-BCS	FACT-BCS+4	BCQ	Breast-Q	SWBCO	FACT-ES	BCPT	MenQOL
Conceptual framework	high	high	high	high	high	high	med	med	high	high	high	high
Target population	med	med	med	high	high	high	med	med	med	med	med	med
Test-retest reliability	high	high	med	unknown	high	high	unknown	high	unknown	high	unknown	high
Internal consistency	med	med	high	med	med	med	high	high	high	high	med	high
Content validity	high	high	high	high	high	high	high	high	med	high	high	high
Construct validity	high	high	med	med	high	high	med	unknown	unknown	high	high	unknown
Ability to detect change	high	high	high	high	high	high	high	unknown	unknown	high	unknown	high
Interpretability	med	med	med	med	med	med	med	med	med	med	med	med
Translation	high	high	low	high	high	high	low	med	low	high	unknown	med
Number of items	30	27	59	23	10	15	30	32-114*	6	19	18	32
Time to complete (min)	10	5-10	5-15	10*	10*	10*	10-15	10-20*	5	10	5-10	7
Administrative burden	high	high	high	high	high	high	med	high	high	high	high	high
Licensing	high	high	low	high	high	high	med	high	high	high	high	high
Locations in use	high	high	low	high	high	high	low	high	low	high	med	med
Number of citations	high	high	med	med	high	low	med	med	low	med	low	med
Year developed	med	med	med	med	med	high	med	high	high	med	med	med

Abbreviations: EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core, FACT-G =Functional Assessment of Cancer Therapy-General, CARES-SF = Cancer Rehabilitation Evaluation System-Short Form, EORTC-BR23= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Breast Cancer, FACT-BCS= Functional Assessment of Cancer Therapy- Breast Cancer Subscale, BCQ= Breast Cancer Chemotherapy, SWBCO = Satisfaction with Breast Cosmetic Outcomes, FACT-ES= Functional Assessment of Cancer Therapy-Endocrine Subscale, BCPT = Breast Cancer Preventive Trial Symptom Scales, MenQOL = Menopausal Specific Quality of Life

[a] The psychometric quality of each PROM was evaluated, based on the International Society for Quality of Life Research (ISOQOL) criteria

eTable 9. Overview of domain coverage of patient reported outcome measurements (PROMs)

	Health-related quality-of- life (HRQOL) Instruments										
	Cancer specific QoL			Breast cancer specific		Breast cancer treatment specific					
Outcomes	EORTC-C30	FACT-G	CARES-SF	EORTC-BR23	FACT-BCS+4	BCQ	Breast-Q[a]	SWBCO	FACT-ES	BCPT	MenQOL
Nr of items covering outcomes	21/30	25/27	35/59	14/23	12/15	14/30	4-16	7/7	12/19	12/18	27/32
Overall well-being	2	1									
Physical functioning	4	7	10			1					2
Emotional functioning	2	3				5					
Cognitive functioning	2		1							3	1
Social functioning	2	6	17			2					7
Ability to work	1	2	1			1					
Anxiety	1	1	1		2	1					1
Depression	1	2				1					1
Financial impact	1										
Pain	2	1				1				1	3
Fatigue	3	1	1			1					1
Sexual functioning		1	3	3					2		2
Body image			1	4	5	1		3		1	3
Satisfaction with breasts							4-16	4			
Arm symptoms				3	5					2	
Breast symptoms				3					2		1

eTable 9. Overview of domain coverage of patient reported outcome measurements (PROMs) (*continued*)

	Health-related quality-of- life (HRQOL) Instruments										
	Cancer specific QoL			Breast cancer specific		Breast cancer treatment specific					
Outcomes	EORTC-C30	FACT-G	CARES-SF	EORTC-BR23	FACT-BCS+4	BCQ	Breast-Q[a]	SWBCO	FACT-ES	BCPT	MenQOL
Vasomotor symptoms				1					3	2	3
Peripheral neuropathy											
Vaginal symptoms									4	2	1
Arthralgia									1	1	1

Domain covered by instrument (number of questions)

Domain not covered by instrument

Abbreviations: EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core, FACT-G =Functional Assessment of Cancer Therapy-General, CARES-SF = Cancer Rehabilitation Evaluation System-Short Form, EORTC-BR23= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Breast Cancer, FACT-BCS= Functional Assessment of Cancer Therapy- Breast Cancer Subscale, BCQ= Breast Cancer Chemotherapy, SWBCO = Satisfaction with Breast Cosmetic Outcomes, FACT-ES= Functional Assessment of Cancer Therapy-Endocrine Subscale, BCPT = Breast Cancer Preventive Trial Symptom Scales, MenQOL = Menopausal Specific Quality of Life

eTable 10. Results of item scores by respondents of feedback survey

Statements on Breast Cancer Standard Set	% rating "very confident" (score 7-9)	Mean score	Comments[a]
Part I. High level overview of Standard Set			
The Breast Cancer Standard Set represents a comprehensive overview of the most essential outcomes for patients with BC.	63%	7.0	No outcomes specific to end of life care are included.
The in- and exclusion criteria cover the population sufficiently with treatment approaches that are considered standard of care.	74%	7.5	
The outcomes are sufficiently parsimonious to be collected routinely by patients and clinicians.	54%	6.5	Number of PROM items could lead to compliance issues in daily practice. Disutility of care could be shortened as complications are relatively uncommon in BC care and might not be useful for benchmarking.
Time points for measurement are feasible to follow up patients.	57%	6.2	Collecting long-term outcomes would require good IT support
The case-mix factors are appropriately comprehensive to enable risk-model development for provider performance comparison.	57%	6.3	
I agree with recommend tools, questions and methods.	71%[b]		
Part II. Complete overview of Standard Set			
Case-mix factors are defined properly, are comprehensive enough to enable risk-adjustment and can be collected in clinical practice.	62%	6.6	
Items of patient-reported form are comprehensive enough to cover PRO domains and can be collected by patients.	72%	6.7	It could be challenging to have patients complete all PROMs

eTable 10. Results of item scores by respondents of feedback survey (*continued*)

Statements on Breast Cancer Standard Set	% rating "very confident" (score 7-9)	Mean score	Comments[a]
Clinical outcomes and treatment approaches are defined properly and can be collected in routine clinical practice.	62%	6.5	Reoperation due to involved margins was considered a debatable measure for quality of care because it also relates to patient wishes and could create wrong incentives.

The online feedback survey consisted of two parts: 1) high-level overview of the Set for review of a summary of the recommended outcomes, treatment approaches, case-mix factors and in- and exclusion criteria. 2) complete overview of the Standard Set with access to the complete Reference Guide in order to review each variable with corresponding definitions and response options. Respondent had to rate their confidence on a 9-point Likert scale (e.g. 7-9 was very confident)

[a] Total of 35 healthcare professionals completed the survey, including 16 surgeons, 8 statisticians and researchers, 4 medical oncologists, 2 nurses, 1 radiation oncologist, 1 radiologist, 1 plastic surgeon and 1 consultant)

[b] Response option was binary ("yes/no") instead of the 9-point Likert scale

eTable 11. Types of treatment modalities and treatment-specific acute complications and long-term morbidity

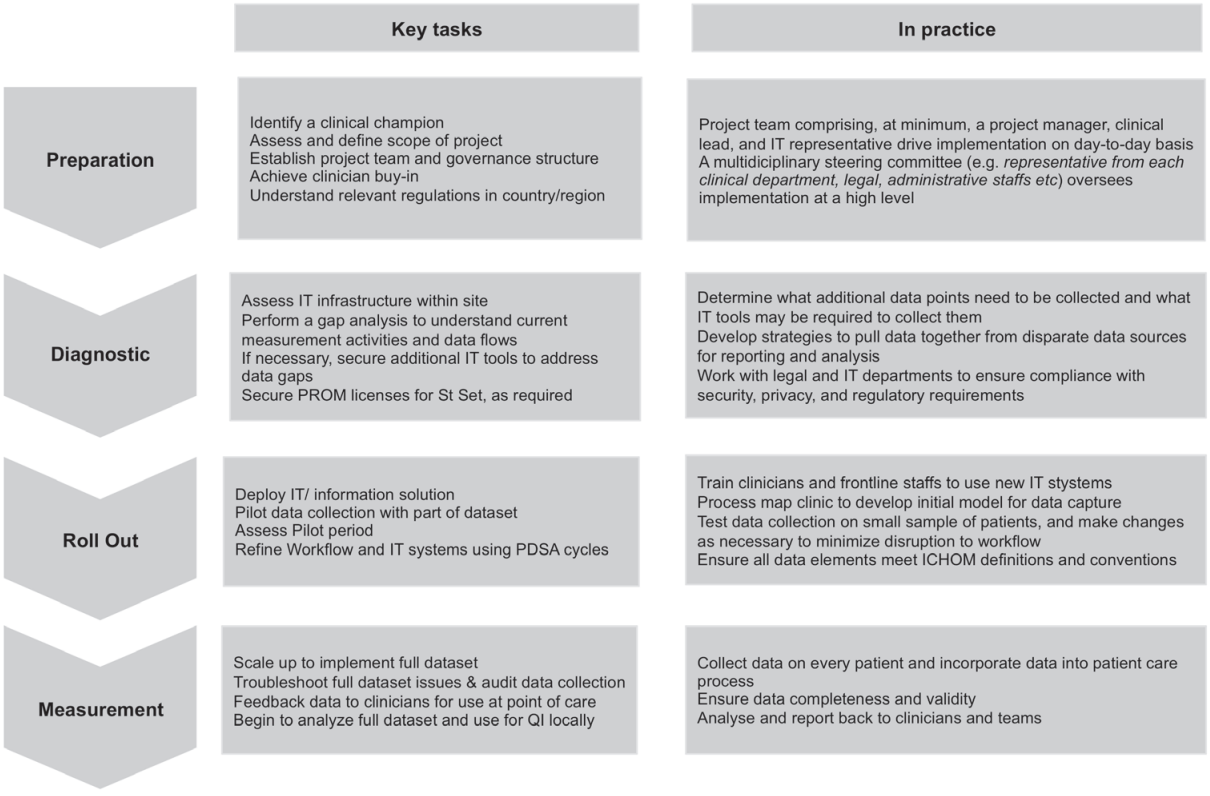
Baseline		Short-term follow-up- clinically reported[a]		Long-term follow-up - PROMs[b]
Category	**Treatment modality**	**Severity of acute complication**	**Name of acute complications**	**Long-term morbidity**
Local therapy	Surgery (with reconstruction) Surgery to axilla Delayed reconstruction	Any complication leading to: Requiring intervention[c] Prolonged hospitalization[d] Unplanned readmission MC/ICU management Discontinuation of treatment Reduce dosing Death	Wound infection	Breast symptoms Arm symptoms Breast satisfaction Fatigue Pain
			Seroma/hematoma	
			Mastectomy skin flap necrosis	
			Hemorrhage	
			Autologous flap loss/ necrosis (total/partial)	
			Implant loss	
			Thromboembolic	
			Nerve damage	
			Delayed wound healing/ dehiscence	
	Radiotherapy		Skin toxicity	
Systemic therapy	Chemotherapy Targeted therapy		Pneumonia Neutropenic sepsis Thromboembolic	Neuropathy Arthralgia Fatigue
	Hormonal therapy		Thromboembolic	Hot flashes Menopausal symptoms

[a] Collection of acute complications is recommended whilst the patient is undergoing treatment or within 90 days of treatment completion, except for complications of hormonal therapy which will be collected up to 1 year

[b] Tracked via patient-reported outcome measurements (PROMs) annually, up to 10 years

[c] Including surgical, radiological and endoscopic interventions

[d] Defined as a hospital stay of more than 14 days



eFigure 2. Phases involved in implementation of the Standard Set

8 General discussion and future perspectives

GENERAL DISCUSSION

In most western healthcare systems, over the last decade major efforts have been made to monitor and improve the quality and effectiveness of cancer care. Assuring quality via nationwide clinical audits has proved to be a powerful tool to gain insight in the quality of care and to facilitate quality improvement. In the context of the rapid advancements in new anticancer drugs, the trends in multidisciplinary cancer care and the focus towards patient-centred outcomes, assurance of quality needs to evolve constantly to anticipate to these changes. This thesis aims to investigate how quality could be assured facing these trends in cancer care.

Part I: Assuring quality in multidisciplinary cancer care

Hospital variation in medical oncology

The majority of DICA audits have their focus on the quality of surgical treatment and short-term outcomes of care. Risk-adjusted outcomes like postoperative morbidity and mortality are often used to evaluate hospital performance and give an ultimate insight into the quality of surgical care [1] [2]. However, with a growing number of treatment modalities becoming available for many tumour types, auditing the non-surgical component of multimodality therapy becomes increasingly important.

In gastric cancer treatment, Dutch guidelines recommend perioperative chemo(radio) therapy for patients with resectable gastric cancer who are eligible in terms of physical condition and comorbidity [3]. We have observed considerable hospital variation in the use of adjuvant chemo(radio)therapy in gastric cancer patients, even after random variation and case-mix correction [**this thesis**]. This suggests that the variation is not merely a reflection of age or comorbidity burden, but it may also reflect other (hospital specific) factors.

However, as the DUCA has its focus on the quality of surgical treatment and short-term outcomes of care, detailed information is missing on the adjuvant component and long-term outcome data is not registered. Moreover, hospital-specific quality data in relation to the national average is only fed back to the participating surgeons. Because the underlying cause of the variation could not be further investigated, an in-depth investigation in hospitals was performed with the aim of identifying organizational and process factors associated with the use of multimodality treatment

[4]. A multidisciplinary extension of the DUCA with medical oncologists, radiation oncologists, pathologists and gastroenterologists may offer a better understanding in the decisional process and quality of multimodal treatment from the audit itself and would facilitate such in-depth investigations. All disciplines would then be provided with benchmarked feedback, including oncologists and radiologists who play a major role in the multimodal treatment of gastric cancer patients.
Fortunately, (surgical) DICA audits are slowly transforming to multidisciplinary condition focused audits. The DSCA is converted to the multidisciplinary Dutch ColoRectal Audt (DCRA) as radiotherapists, gastroenterologists, medical oncologist and radiologists joined the audit. In addition to data collection of patient undergoing resections for colorectal cancer, patients with a wait-and-see strategy after initial treatment with (chemo)radiotherapy, with or without surgery, for rectal cancer are now registered.
A true condition focused audit in which multiple treatment strategies are registered by the relevant disciplines has been created for lung cancer: the Dutch Lung Cancer Audit (DLCA), in which radiotherapist, surgeons and pulmonologists participate. In addition, linkage of data from the DUCA and DCRA with long-term survival data from Vektis, a database containing data from all Dutch healthcare insured Dutch citizens, is recently realized.
Although challenging with regards to linkage of databases, privacy issues and registration burden, only such multidisciplinary condition focused audits including survival data would create a better understanding on the quality of multimodal treatment in cancer patients and it's impact on long-term survival. In future, with the increasing population of old and frail cancer patients it would be extremely valuable to track the outcomes of patients who receive palliative treatment or no treatment at all.

Multidisciplinary outcomes
Multidisciplinary tumour boards have become the hallmark for cancer care and have been rooted in everyday practice [5]. In the Netherlands, such multidisciplinary boards have developed evidence-based guidelines on the treatment of many tumour types [3]. In addition, the Dutch federation of oncological societies (SONCOS) has set up multiple multidisciplinary quality standards listing requirements a cancer centre must meet [6]. Although cancer care is increasingly becoming a multidisciplinary undertaking, benchmarked feedback via audits is mainly discussed monodisciplinary in Dutch hospitals. For instance, surgeons only discuss postoperative complications

with their peers. However, adverse outcomes can transcend disciplines [**this thesis**]. We showed that gastric cancer patients with severe postoperative complications had an increased likelihood of adjuvant chemotherapy omission. In hospitals with the lowest administration rate, adjuvant chemotherapy was three times more likely to be omitted compared to the national average. It is unlikely that the omission of chemotherapy can be fully attributed to postoperative complications or frailty of patients. Differences in the expertise of the medical team to recognize and adequately treat complications to ensure patients are fit enough for postoperative chemotherapy might also play a role. The considerable variation might also reflect differences in the culture or communication between surgical and medical departments. It would therefore be valuable to discuss such multidisciplinary quality measures in multidisciplinary team meetings within hospitals on a regular basis. This could stimulate shared accountability and ultimately enhance joint quality initiatives.

Part II: Assuring quality in precision medicine

Value of registries in medical oncology: appropriate drug use and safety surveillance

The treatment of metastatic melanoma has been revolutionized with the introduction of the BRAF inhibitor vemurafenib and immune checkpoint inhibitor ipilimumab [7]. Since the approval of ipilimumab in 2011 [8] and vemurafenib in 2012 [9] by the European Medicines Agency (EMA), more than seven new drugs are registered for the treatment of metastatic melanoma [10]. These developments indicate the speed with which changes in anticancer therapies are occurring.

The societal challenge is to combine the development and availability of promising new anticancer drugs with the sustainability of our healthcare system. Current checkpoint inhibitors have a list price near 60.000 Euro per year [10]. These promising drugs have also been approved for many other cancers, such as metastatic lung cancer, renal cell cancer, head and neck cancer, bladder cancer, Merkel cell carcinoma, various types of lymphomas, and others will follow soon. As a result of the rapidly evolving treatment landscape of oncologic care together with the aging population and growing number of cancer survivors, the sustainability of cancer services as part of national health systems has become a major challenge. In the Netherlands, the prediction is that around 23 billion euro will be spent on cancer treatment by 2040, over four times as much as in 2015 [11].

In response to this, a special committee of the Dutch Cancer Society (KWF) investigated the accessibility and affordability of expensive anticancer drugs [12]. In their report, they advocate set-ups of registries like the DMTR as it gives insight into real-world cost-effectiveness of treatments and treatment-patterns. First results from the DMTR demonstrate that the new drugs for metastatic melanoma have been safely introduced in the Netherlands with comparable toxicity rates as reported in the pivotal trials [**this thesis**]. This may be attributed to the centralization of advanced melanoma care into fourteen specialized melanoma centres and the obligatory minimum volume standard of 20 melanoma patients yearly [13]. Registries like the DMTR are therefore important to inform policy makers whether interventions work in real world.

Bearing the high costs and potentially life-threatening side effects of the new drugs in mind, defining subgroups of patients who benefit most is of great importance.
This thesis demonstrated that metastatic melanoma patients with a baseline lactate dehydrogenase (LDH) of >2x the upper limit of normal (ULN) who respond to targeted therapy with normalization of LDH have a good chance to get durable response on immunotherapy [**this thesis**]. If LDH remains elevated, immunotherapy does not stand a chance. After a median follow-up of 22 months, we demonstrated that median OS from start of immunotherapy was not reached in the former group while median OS was only 0.9 months in the latter group. This information can be used to determine the optimal sequencing of various drug types in a real-world setting, while the pivotal trials only report on the investigational drug. Although randomized trials are needed to assess the real benefit of sequential treatment strategies, results from the DMTR can be of added value while trial results are yet to be published.

Combining risk factors instead of assessing them separately as has been done in the pivotal trials could be helpful to stratify patients into favourable or poor prognosis groups. Almost 70% of metastatic melanoma patients treated with vemurafenib had multiple risk factors, such as an elevated LDH level, symptomatic brain metastases and poor performance status [**this thesis**]. We demonstrated that survival of BRAF-mutated advanced melanoma patients treated with vemurafenib having >3 risk factors was only a third of the survival of patients without any risk factors (5.4 months *vs* 15.4 months). From a patient and doctor perspective, these data can help in shared

decision making and managing expectations. In patients with multiple risk factors, the drug has a low probability of benefitting the patient and may instead be physically and mentally harmful with wasted costs to the health system. This knowledge can nourish the debate on appropriate drug use.

In response to political and societal pressure, the FDA and EMA have introduced numerous fast-track approval and adaptive pathways for new anticancer drugs since the beginning of the 21st century [14]. Conditional approval may benefit patients by speeding up the availability of 'promising' drugs, but on the other hand are not based on profound evidence of a phase III randomized clinical trial. Such drugs may be studied with smaller patient numbers or in single-arm studies with no comparator [15]. In addition, cancer drug approvals based on surrogate outcomes (e.g. progression free survival) have become more common leading to faster drug access and lower trial costs, but are not always reliable surrogates for improved survival or QoL, in particular in non-curative settings [16]. Together with the fact that trial results are not generalizable to a more heterogeneous patient population in daily practice, great uncertainties regarding clinical benefit and safety remain at time of drug approval.
Real-world registries could complement findings from trials and could provide a better understanding of a drug's real world value after (fast-track) approval [17]. Registry data can hence be helpful to detect approved drugs that fail to demonstrate clinical benefit or harm patients in real world which warrant further investigations or even requires withdrawal from the market.

DMTR: a blueprint for quality assurance in the era of expensive anticancer drugs?
First results of the DMTR showed the value and feasibility of nationwide registries with new anticancer therapies, as demonstrated by high quality data and nationwide coverage of all patients with metastatic melanoma in the registry within the first year [**this thesis**].
Downside of such a multipurpose registry like the DMTR is the financial and administrative burden. Although detailed data for economic evaluation (informal care, productivity losses) are only collected in selected melanoma centres, the majority of data (clinical, economic, PROMs) are collected for all metastatic melanoma patients. This approach adds a lot to time and costs. One patient record requires 8 hours of registration, including data-entry, validation, data-analyses, reporting and training

of the data managers. Questions could be raised whether this set-up could serve as a blueprint for future registries. For instance, immunotherapies are now approved for lung cancer with over 10.000 eligible patients every year (in contrast to 800 eligible metastatic melanoma patients per year).

To minimize registration burden, a solution may be to use multiple datasets. A small dataset will be collected for all patients to track trivial quality data such as case-mix factors, treatment modality, QoL, mortality and morbidity, whereas additional limited datasets will be collected in a subsample for other purposes like cost-effectiveness. For cost-effectiveness models, cost data of a very small subset can easily be extrapolated because only mean values of costs are required [18].

Second, it needs to be stimulated to evaluate all data items on its added value on a regular basis. Since the landscape of immunotherapy and targeted therapy is evolving rapidly, (detailed) data items of certain treatment modalities can soon be outdated.

Third, data-entry accounts for the majority of the time and costs of the DMTR because data managers manually enter the data by searching though the EHR. Initiatives such as data capture at the point of care (e.g. Registratie aan de Bron) allow registries to obtain (part of) their data directly from EHRs [19]. For instance, head and neck surgeons of Radboudumc have succeeded to reorganize their EHR in such a way that all 150 items required for quality indicators of the Dutch Head and Neck Audit are directly obtained from EHRs. Implementation of such EHR systems could further reduce financial and administrative burden.

Last, a large amount of the dataset of the DMTR is collected to facilitate reimbursement research. In The Netherlands, new expensive drugs can be reimbursement conditionally in order to guarantee early access to promising drugs since 2016. In exchange, it is obliged to gather data on real-world cost-effectiveness. A reassessment of a drug's real-world value after 4 years determines whether additional financing will continue [20]. During this period, a large amount of additional data has to be gathered through the patient registry (e.g. data on hospital resource, non-medical costs).

Assessment of the best time for definite reimbursement decision rather than setting a fixed 4-year period could avoid costly and time-consuming data gathering. Statistical methods have been proposed to calculate the optimal length of registry period based on patient numbers, costs and outcomes. A recent study showed that the observation period to make the definite reimbursement decision on the use of oxaliplatin for

colon cancer could have been stopped after a maximum of 2 years rather than the fixed 4 years [21].

It should also be noted that the costs of multi-purpose quality registries like the DMTR are a fraction of the total costs of the new drugs. The National Health Care institute calculated that less than 1% of the total amount of costs per treated advanced melanoma patient would be required for the set-up and maintenance of the DMTR. It will be important to all stakeholders involved to discuss whether securing a small percentage of the total treatment budget for obtaining quality information for future registries would be acceptable.

Part III: Assuring quality focusing on patient centred outcomes

VBHC auditing– the way forward?

Understanding the effect of treatment on how a patient survives, feels or functions is crucial [22]. Although anticancer treatment has brought major advances in patient survival rates, it is also associated with significant toxicity that can impair quality of life (QoL). The impact on QoL can only be understood by collecting information directly from patients about their physical functioning, adverse events or cancer-related symptoms. Despite growing interest in patient reported outcome (PROs) measures in cancer care, drug developers and physicians do still not systematically collect PROs in pivotal trials or clinical practice [23]. The majority of pivotal trials publish PRO results in separate papers as if it is not important when balancing the risks and benefits of new drugs [24] [25]. This way, true shared decision-making between patients and oncologists is hampered by lack of reliable and acceptable PRO data.

This thesis illustrates the 'blind spot' of collecting merely clinical outcomes. We have demonstrated that benefit of vemurafenib was unlikely in frail advanced melanoma patients with a high disease load in terms of overall survival [**this thesis**]. Since vemurafenib could induce rapid symptom relief in this subgroup of patients [26], the emphasis lies however predominantly on improving quality of life (QoL). Without such information, we are left with an incomplete picture on the properties of this drug. Fortunately, the DMTR is currently collecting QoL data in order to assess the true benefit of the new anti-melanoma drugs in daily practice, which will eventually

lead to better shared decision-making. The importance of collecting PRO data has been acknowledged by other DICA audits of which eight are currently collecting PROMs.

Many tumour types can increasingly be seen as a chronic disease. In The Netherlands, the 5-year overall survival of cancer patients is almost doubled in the past 50 years (Figure 1), where traditional outcome measures such progression-free and overall survival are less relevant, and quality of life and functional outcomes will be more valued. As a result of having had cancer and its treatment, cancer patients and survivors are affected by gastrointestinal problems, sexual dysfunction, pain, lymphedema, chronic fatigue, depression, and so on. A wider recognition of cancer care as a chronic disease is required in quality assessment programmes.
This has been acknowledged by the International Consortium for Health Outcomes Measurement (ICHOM) that recently launched a patient-centred outcomes set for patients with colorectal cancer and breast cancer [**this thesis**]. The ICHOM standard sets encompass the entire care spectrum, from diagnosis, treatment, short- and long-term outcomes to end-of-life care. Patient-reported outcomes are included in every standard set to capture symptom burden, functional status and health-related quality of life. The ICHOM breast and colorectal standard set comprises fourteen patient-centred outcomes of which the majority (70%) is patient-reported (Figure 2). DICA has started to synchronize its datasets with the ICHOM standard sets, including the incorporation of PROMs recommended by ICHOM. Such monitoring and comparison of patient-centered outcomes can identify opportunities for improvement and ideally, lead to a sharing of best practices within the full range of cancer care. Moreover, international comparison with other (nationwide) registries can be achieved.

Although the VBHC principle has been embraced in multiple countries, there are also reasons to be cautious.
In contrast to existing surgical audits where short-term outcomes like anastomic leakage after colorectal surgery are clearly linked to interventions [1], patient-centred outcomes like fatigue or sexual functioning after breast cancer treatment are likely to be multifactorial. It is harder to accurately assess case-mix variables as these outcomes can also be influenced by other factors than patient- and tumour characteristics such

as societal and financial characteristic or supportive therapies such as psychological treatment.
Secondly, ICHOM standard sets only focus on outcomes, while process measures like waiting times or completeness of pathology report are not included. These measures are however important to identify the critical steps in a process that lead to a particular outcome (quality assessment). This way care providers accountable for these steps can be determined. In order to set-up quality improvement initiatives, negative outcomes as defined by the ICHOM standard set must be distilled to its essence by identifying these steps.
Moreover, patient-reported experience measures (PREMs), which capture a patient's view of what happened during the care process, were not included in the ICHOM standard sets. Cancer care nowadays has become an integral part of the lives of most cancer patients and survivors, and experience measures such as autonomy, choice, communication and support (access to family and community support networks) are increasingly be seen as important measures of the effectiveness of healthcare [27]. This was also demonstrated by the results of the patient validation survey of the ICHOM breast and colorectal standard sets. In both sets, 20% of patients believed additional outcomes on experience measures had to be included [**this thesis**]. The ultimate model might be a hybrid model where the most important process measures (clinical and PREMs) and (long-term) patient-centred outcomes (clinical and PROMs) are collected.

Although PROMS data has proved to be highly wanted for assuring quality in cancer care [28], more research is needed on the feasibility of collecting PROMs in daily practice. For instance, since 2013 Santeon, a Dutch network of seven hospitals, collects PROs systematically for prostate cancer and lung cancer but compliance rates of only 20-25% have been reported [29].
One explanation might be the significant patient burden of the questionnaires. The majority of existing questionnaires are primarily designed for clinical trials resulting in lengthy, static and old-fashioned surveys. For instance, the ICHOM dataset on breast cancer recommends the collection of (part of) multiple PROMS ranging from 59-82 questions [**this thesis**], which could be discouraging. Multiple organizations focusing on PROM development are currently developing computerized adaptive testing (CAT) versions, which should reduce respondent burden [30]. On the

other hand, previous studies showed that the number of questions is not the primary reason for non-compliance [31]. Problem areas are more related to implementation practices, such as reminder issues or user-unfriendly PRO design. The use of modern technology for data capture may reduce the frequency of these issues, such as completion of electronic PROs (ePROs) via tablets, cell phones and computers including online reminders [32]. Moreover, staff commitment and education with regards to integration of PRO collection efficiently in daily practice is crucial for successful data collection.
Another issue might be that PROs are mostly used for scientific purpose and results are not fed back to the patients. If PROs are used to detect symptom worsening and would alert physicians during consultations, patients are more willing to complete the (lengthy) questionnaires [33]. A recent trial even found a survival benefit of 5 months with symptom-monitoring via ePROs including feedback compared with usual care in patients with metastatic cancer [34].

FUTURE PERSPECTIVES

Clinical auditing outside the traditional boundaries of medical specialties and hospitals
Although clinical auditing is increasingly shifting from monodisciplinary to multidisciplinary and condition-focused audits, most audits are set-up within the boundaries of medical specialties. However, the role of nurse specialists and allied healthcare professionals such as psychologists, physiotherapists, and dietitians in cancer care has increased. These disciplines are likely to contribute to patient outcomes, in particular on QoL and functional aspects. For instance, the Dutch guideline on breast cancer recommends physiotherapeutic treatment in patients who have undergone axillary treatment as it could have beneficial effects on functional complaints and lymphedema [35]. Dietary issues and management by a dietician were considered highly important by colorectal cancer patients who were involved in the development of the ICHOM colorectal cancer standard set [**this thesis**].
The Dutch Head and Neck Audit is the first DICA audit that gathers quality indicators from the perspective of allied health professionals in addition to the perspective of the medical specialties and patients. First results showed it is challenging but feasible to create quality indicators and collect data from allied health professionals [36].

Complementing quality data of the standard medical therapies with data of supporting therapies will give us insight in the quality of all aspects of cancer care. This way, we could assess the impact of supporting therapies, learn from other disciplines and motivate collaboration even more.

The ICHOM breast and colorectal standard sets created a focus towards cancer survivorship with the inclusion of long-term clinical and PRO data. However, these data is solely collected during or in between outpatient visits within a hospital setting. In the Netherlands, substitution of (cancer) care is high on the political agenda in order to keep care affordable. One main goal is the transition of follow-up visits of cancer survivors that are not required at a high level of care, to primary care practices [37]. Transitioning care for low-risk cancer survivors from oncologists to primary care physicians is found to be safe and cost-effective in other countries [38]. This transition would be a major influence on the organization of cancer care and it would be important to track and understand the impact on patient outcomes, such as QoL, emergency visits, hospital admissions, recurrence and survival outcomes.
Quality measurement is not new for primary care in The Netherlands. Several quality indicators exist for patients with chronic illness, such as diabetes and COPD for internal and external use [39] [40]. One of the aims is to assess whether the coordination of diabetes and COPD care into coordinated multidisciplinary care groups in primary care has helped improving the quality and has lowered the costs [41].
Measuring quality of care in primary care practices could help justify such changes and transitions and could guide further improvement and collaboration between care providers in hospitals and primary care practices.

Big data technologies to assure quality
Several efforts have been made in order to enhance data quality and to reduce registration burden for physicians. Some hospitals have reorganized their EHRs in such a way that required data for clinical auditing could be automatically extracted. Moreover, existing databases are connected to clinical audits to obtain relevant data once, such as the linkage of PALGA, the national database of pathology results, with the DCRA so that pathology data can directly be entered into the DCRA. However, database linkage is not possible for all data items and different IT systems across hospitals make it difficult to introduce automated data subtraction on a national level.

Furthermore, IT systems are primarily build to support daily practice and don't have an (financial) incentive to make it as effective for quality purposes. These barriers could hinder expansion to condition-specific audits in the future.
Although uniform data collection for multiple purposes needs to be stimulated, rapid advances in health information technology (HIT) have created opportunities to collect, aggregate and analyze large amounts of real-world data in unconnected servers, unstructured notes in EHRs and other sources such as claims databases [42]. This could help overcome the wide variation that exists between EHR data standards. Rapid-learning systems could examine all available information on patient characteristics, genetics, treatments, outcomes and costs. It could serve a variety of purposes, ranging from quality improvement to data driven guidelines and clinical decision support tools based on a vast amount of observational data. Rapid-learning systems in different forms already exist within oncology, such as CancerLinQ created by ASCO [43]. Although the published literature on the practicality and results of such systems remain quite preliminary [44] and privacy and juridical issues have to be managed, the potential impact of big data in assuring quality is evident.

END CONCLUSIONS

This thesis showed that the multi-purpose design of the DMTR could be used as a blueprint for future quality initiatives in the era of rapid advancements in immunotherapy and targeted therapy. It could complement findings from trials, as it provides information on long-term (functional) outcomes and optimal sequencing of drugs in a heterogeneous patient population that are normally excluded from trials. The new drugs are becoming a larger part in medical oncology as the number of immunotherapies and targeted therapies increases for a growing number of tumour types. Together with the rise of early access programmes of new expensive drugs, registries like the DMTR are highly needed for cost-effectiveness analyses and to accurately assess the safety and real-world benefit of these drugs.
Notwithstanding, efforts should be made to minimize registration and financial burden to such a level that the balance between practical feasibility and data quality and reliability is optimal.

Furthermore, this thesis showed that important quality outcomes could transcend disciplines. The expansion from monodisciplinary to condition-focused audits is therefore a welcoming development and hopefully, this will stimulate discussions of benchmarked feedback in a multidisciplinary setting within hospitals and facilitate joint quality initiatives.

The breast and colorectal cancer standard sets of ICHOM incorporate outcomes of almost a full cycle of care, from diagnosis to treatment and long-term survivorship, with an emphasis on patient-reported outcomes. While these sets stretch the capabilities of most hospitals, the integration of PROs in daily practice with direct feedback to the patient during outpatient visits may improve the experience, efficiency and outcomes of care. The sets are intended to facilitate international comparisons and research on quality of care outcomes. Monitoring and comparison of outcomes can identify opportunities for improvement and ideally, lead to a sharing of best practices and improvement in patient outcomes.

FIGURES

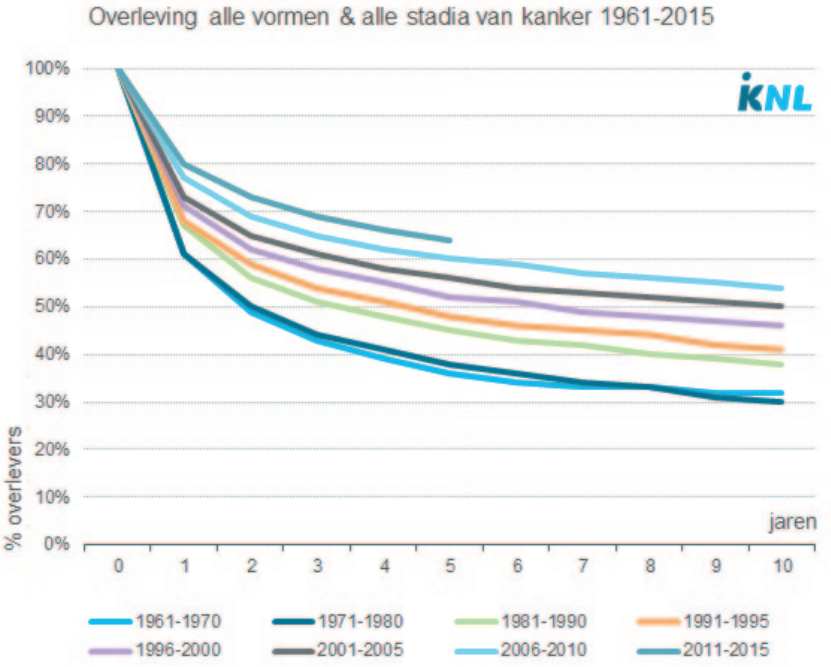
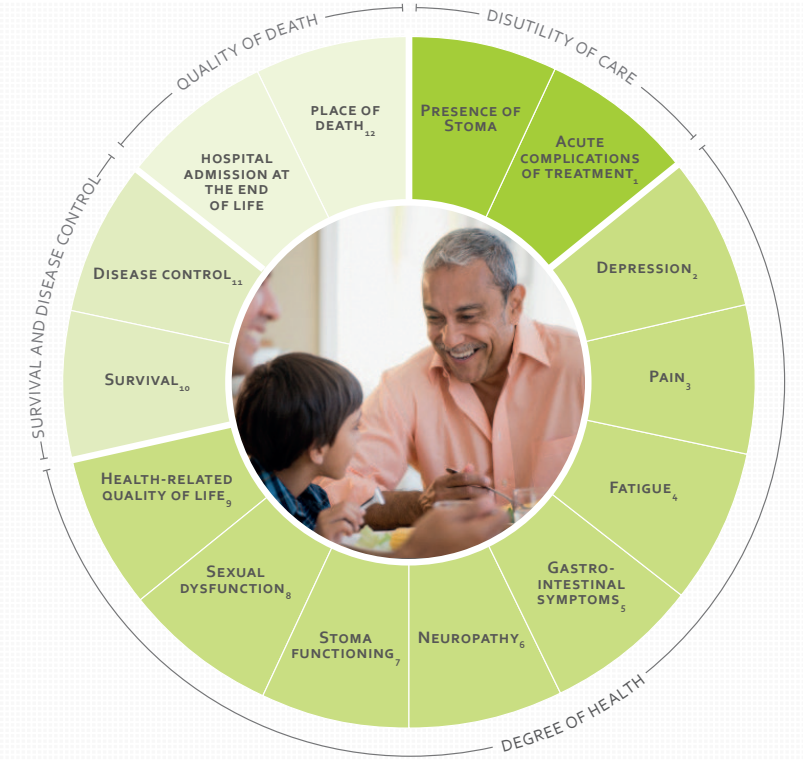


Figure 1. Overall survival of all tumour types in The Netherlands (1961-2015). Source: IKNL



(a)

Figure 2. The ICHOM standard set outcomes wheels for colorectal cancer (a) and breast cancer (b), detailing the outcome domains within the Standard Set.


SURVIVAL AND DISEASE CONTROL
DISUTILITY OF CARE
DEGREE OF HEALTH
RECURRENCE FREE SURVIVAL
SURVIVAL 13
REOPERATION DUE TO POSTIVE MARGINS
ACUTE COMPLICATIONS OF TREATMENT 1
DEPRESSION 2
PAIN 3
FATIGUE 4
BODY IMAGE 5
ARM AND BREAST SYMPTOMS 6
VASOMOTOR SYMPTOMS 7
NEUROPATHY 8
ARTHRALGIA 9
FINANCIAL IMPACT 10
SEXUAL DYSFUNCTION 11
HEALTH-RELATED QUALITY OF LIFE 12

(b)

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9 Dutch summary

EEN GEÏNTEGREERDE KIJK OP KWALITEITSMETING VAN MULTIMODALE THERAPIE IN DE ONCOLOGISCHE ZORG

Er zijn grote ontwikkelingen gaande binnen de oncologische zorg. Kankerzorg is een steeds complexere medische discipline met een grote hoeveelheid aan specialismen en paramedici die betrokken zijn in het zorgproces.
Daarnaast hebben de opkomst van immunotherapie en doelgerichte therapie een ware revolutie teweeggebracht in de oncologie. Doelgerichte therapie blokkeert de groei en deling van kankercellen doordat ze de werking tegengaan van specifieke moleculen die de kankercellen nodig hebben voor hun groei en overleving. Immunotherapie verandert het eigen afweersysteem zodat het beter in staat is om kankercellen te doden. Deze nieuwe behandelmethodes hebben de overlevingskansen van veel oncologische patiënten sterk verbeterd; de groep patiënten die kanker heeft overleefd groeit enorm.
Ten slotte neemt personalised medicine ofwel 'therapie op maat' een steeds belangrijke plaats in binnen de oncologie. Hierbij wordt de meest succesvolle behandeling voor een individuele patiënt bepaalt op basis van specifieke karakteristieken van de patiënt of tumor, zoals bepaalde mutaties van een tumor.
Al deze ontwikkelingen zorgen voor een nieuwe kijk op kwaliteitsmeting van oncologische zorg. Dit proefschrift beschrijft hoe kwaliteitsmeting kan worden verricht in dit nieuwe tijdperk.

Deel 1. Kwaliteitsmeting in multidisciplinaire kankerzorg

Al enkele jaren wordt het belang van professionele kwaliteitsmeting van de oncologische zorg in de vorm van clinical auditing in Nederland onderstreept. Clinical auditing heeft als doel het zorgproces en de uitkomsten van de zorg inzichtelijk te maken en continue te verbeteren. In 2009 is de Dutch Surgical Colorectal Audit (DSCA) opgericht om de kwaliteit van de darmkankerchirurgie inzichtelijk te maken. De DSCA bleek een krachtig kwaliteitsinstrument waarbij er binnen enkele jaren aanzienlijke verbeteringen zijn opgetreden in het zorgproces en in de uitkomsten van darmkanker patiënten. In navolging op het succes van de DSCA zijn er veel soortgelijke kwaliteitsregistraties opgericht, gefaciliteerd door de Dutch Institute for Clinical Auditing (DICA).

Clinical auditing werd jarenlang vooral gebruikt in de chirurgische oncologie. Echter, multimodale therapie, waarbij naast chirurgie ook andere therapievormen worden gebruikt zoals radiotherapie en chemotherapie, is de afgelopen jaren de hoeksteen geworden in de behandeling van veel tumorsoorten. In tegenstelling tot de grote hoeveelheid internationale literatuur over de kwaliteit en variatie van de chirurgische behandeling van oncologische patiënten, is er over de kwaliteit en variatie van de multimodale therapie betrekkelijk weinig bekend.

Hoofdstuk 2 evalueert de ziekenhuisvariatie in het gebruik van chemotherapie na een operatie voor maagkanker. De multidisciplinaire richtlijn voor maagkanker adviseert perioperatieve chemo(radio)therapie voor alle patiënten met een operabel maagcarcinoom, mits de conditie van de patiënt dit toelaat. Voor dit onderzoek is gebruik gemaakt van gegevens afkomstig uit de Dutch Upper GI Audit (DUCA). De DUCA werd in 2011 opgericht door de Dutch Oesophageal Cancer Group (DOCG) en de Dutch Gastric Cancer Group (DGCG) met als doel het verkrijgen van inzicht in de kwaliteit van zorg van de chirurgische behandeling van slokdarm- en maagkanker en het in gang zetten van verbetertrajecten.

Het onderzoek toont aan dat er een zeer grote spreiding bestaat tussen ziekenhuizen in het gebruik van postoperatieve chemotherapie bij geopereerde maagkanker patienten die hiervoor in aanmerking komen. Omdat patiënt- en tumorkarakteristieken het gebruik van chemotherapie kunnen beïnvloeden (casemix), is hiervoor gecorrigeerd. In sommige ziekenhuizen was de kans op het krijgen van chemotherapie zeven keer zo groot ten opzichte van het landelijk gemiddelde. Dit onderzoek laat het belang zien van kwaliteitsmeting van niet-chirurgische behandelingen. Omdat de DUCA in opzet een chirurgische audit is, konden eventuele oorzaken die ten grondslag liggen aan deze ziekenhuisvariatie helaas niet verder worden onderzocht. Doordat multimodale therapie een steeds grotere plaats inneemt in de oncologische zorg, kunnen alleen multidisciplinaire, ziekte specifieke audits een complete kijk geven op de kwaliteit van zorg. Gelukkig zijn een aantal chirurgisch georiënteerde kwaliteitsregistraties van DICA uitgebreid tot multidisciplinaire registraties, waarbij ook andere behandelingen, zoals radiotherapie en chemotherapie, worden geregistreerd. Een goed voorbeeld hiervan is de Dutch Lung Cancer Audit, waarbij de verschillende longkankeraudits die elk een andere behandeling registreerde, bij elkaar zijn gevoegd.

Multimodale therapie zorgt daarnaast voor een complexere vorm van kwaliteitsmeting omdat verschillende behandelingen elkaar kunnen beïnvloeden. **Hoofdstuk 2** toont aan dat de kans op het krijgen van chemotherapie drie keer zo klein is voor geopereerde maagkanker patiënten met ernstige postoperatieve complicaties ten opzichte van patiënten zonder ernstige complicaties. Dit onderzoek laat zien dat postoperatieve complicaties niet alleen van invloed zijn op korte termijn uitkomsten, maar ook een negatief effect kunnen hebben op de lange termijn overleving doordat postoperatieve chemotherapie achterwege wordt gelaten. Het is onwaarschijnlijk dat dit geheel ten grondslag ligt aan de kwetsbaarheid van de patiënt. Er is immers gecorrigeerd voor casemix factoren. Waarschijnlijk spelen andere ziekenhuis gerelateerde factoren ook een rol, zoals de expertise van het medische team om een complicatie adequaat op te sporen en te behandelen zodat de conditie van de patiënt goed genoeg is voor chemotherapie. De aanzienlijke ziekenhuisvariatie kan ook een afspiegeling zijn van verschillen in communicatie tussen het chirurgische en oncologische team. Het zou daarom waardevol zijn om zulke discipline overstijgende uitkomsten te bespreken in multidisciplinaire teams met als doel er van te leren en gezamenlijke verbetertrajecten op te stellen.

Deel 2. Kwaliteitsmeting in personalised medicine

Voor een lange tijd was chemotherapie de belangrijkste behandelvorm in het therapeutische arsenaal van medisch oncologen. Het selecteren van patiënten, de behandelschema's en de toxiciteit die de behandeling teweeg bracht, waren min of meer gelijk voor de verschillende tumorsoorten.

De introductie van immunotherapie met immuun-checkpoint-remmers en doelgerichte therapie hebben hier verandering in gebracht.

De eerste ervaringen met immunotherapie werden opgedaan bij patiënten met een gemetastaseerd melanoom.

Vijf tot tien jaar geleden was DTIC, een vorm van chemotherapie, de enige beschikbare behandeling voor patiënten met een gemetastaseerd melanoom. Het melanoom reageerde echter nauwelijks op chemotherapie, waarbij slechts in 5% van de gevallen de groei van de tumor (vaak tijdelijk) tot stilstand kwam. Sinds de opkomst van de nieuwe oncolytica is de overleving van patiënten met een gemetastaseerd melanoom sterk verbeterd. Ipilimumab, een anti-CTLA-4 monoclonale antilichaam, is het eerste immuuntherapeutisch medicijn wat op de markt is gebracht in 2011. De toelating

van BRAF-kinaseremmers vemurafenib en dabrafenib behorend tot de doelgerichte therapie volgde de jaren erna.
Ondanks de positieve overlevingsresultaten, hebben de nieuwe oncolytica ook gezorgd voor nieuwe uitdagingen. De nieuwe geneesmiddelen kunnen ongewone en potentieel ernstige bijwerkingen veroorzaken die expertise vereisen in de herkenning en behandeling hiervan. Verder draagt de opkomst van de dure oncolytica in toenemende mate bij aan de stijging van de zorgkosten. De kosten kunnen oplopen tot wel 60.000 euro per patiënt per jaar. Ook vereist de moleculaire analyse van het melanoom, de indicatiestelling en de sequentie van de verschillende behandeling expertise in de behandeling van het gemetastaseerd melanoom.
De minister van Volksgezondheid, Welzijn en Sport heeft daarom in 2012 enkele eisen gesteld alvorens de nieuwe geneesmiddelen voor het gemetastaseerde melanoom te vergoeden. De systemische behandeling moest worden gecentraliseerd in veertien gespecialiseerde ziekenhuizen verspreid over Nederland, zogeheten melanoomcentra, waarbij verplicht is gesteld dat elk centrum een minimum van twintig patiënten per jaar behandeld. Daarnaast kregen deze centra de verplichting om informatie van alle melanoompatiënten vast te leggen in een register: the Dutch Melanoma Treatment Registry (DMTR).
Dit register, gefaciliteerd door DICA, is opgezet om het gebruik, de effectiviteit en de kosten van de nieuwe middelen in de dagelijkse praktijk te monitoren en te beoordelen.

In **hoofdstuk 3** wordt de unieke opzet van de DMTR en worden de eerste resultaten beschreven. De DMTR heeft meerdere doelen:

- Clinical auditing: door periodieke online terugkoppeling van de kwaliteitsindicatoren aan de melanoomcentra in vergelijking met de andere melanoomcentra en het landelijk gemiddelde, kan de geleverde zorg in kaart gebracht worden en kunnen verbetercycli worden opgesteld;
- Transparantie van zorg: de kwaliteitsindicatoren kunnen worden gebruikt voor externe verantwoording en keuze informatie voor patiënten;
- Doelmatigheidsonderzoek: de beoordeling van het effect van de nieuwe geneesmiddelen in de dagelijkse praktijk, inclusief de gezondheidswinst en de kosten die hiermee gepaard gaan;
- Wetenschappelijk onderzoek.

De studie laat zien dat het gelukt is om een nationale dekking te realiseren binnen één jaar. Daarnaast tonen de eerste resultaten aan dat het percentage ernstige bijwerkingen in de dagelijkse praktijk nagenoeg gelijk is aan hetgeen is gerapporteerd in de gerandomiseerde trials. Mogelijkerwijs heeft dit te maken met de centralisatie van de melanoomzorg in de veertien gespecialiseerde centra. Hierdoor kon uitgebreide ervaring worden opgedaan met de nieuwe middelen. Daarnaast kon de opgedane kennis beter worden besproken tussen de centra en konden nieuwe middelen sneller worden geïmplementeerd in de dagelijkse praktijk.
Ten slotte laten de eerste resultaten een significante verbetering van de overleving zien. De mediane overlevingsduur steeg van 10,1 maanden (95% BI 9,1-11,1) in het eerste registratiejaar naar 12,7 maanden (95% BI 11,6-13,7) in het tweede registratiejaar.

Vele studies hebben aangetoond dat trial data niet zomaar te extrapoleren zijn naar de dagelijkse praktijk omdat trials alleen streng geselecteerde patiënten includeren. Het is dus erg waardevol om gegevens uit de klinische praktijk te gebruiken als aanvulling op de kennis afkomstig uit gerandomiseerde onderzoeken. Omdat de nieuwe oncolytica erg duur zijn en potentieel ernstige bijwerkingen kunnen hebben, is een goede selectie van patiënten die voordeel hebben van het medicijn in de dagelijkse praktijk onontbeerlijk. Doordat een kwaliteitsregister zoals de DMTR een grote hoeveelheid data van heterogene patiëntengroepen bevat, is het mogelijk om relevante subgroepen te evalueren.
Hoofdstuk 4 analyseert subgroepen van melanoompatiënten met bepaalde risicofactoren die behandeld zijn met de BRAF-remmer vemurafenib. Deze studie toont aan dat bepaalde risicofactoren een slechte prognose geven, waarbij niet alleen de klinische conditie van de patiënt (de 'WHO performance status') een belangrijke rol speelt maar ook een aantal tumorkenmerken, zoals het gehalte van het lactaat dehydrogenase (LDH) in het bloed, het totaal aantal metastasen en het hebben van hersenmetastasen. Deze studie laat verder zien dat de uitkomsten van een behandeling met vemurafenib bij patiënten met een gunstig risicoprofiel vergelijkbaar zijn met de resultaten gebaseerd op de klinische trials. De studie toont echter ook aan dat de mediane algehele overleving meer dan halveert voor patiënten met drie of meer risicofactoren in vergelijking met patiënten zonder risicofactoren (5,1 maanden *vs* 15,4 maanden). Omdat het 'real-world' data betreft, kan deze informatie behulpzaam

zijn voor zowel dokters als patiënten bij het maken van een behandelkeuze. In de toekomst zal ook informatie afkomstig van de patiënt, de zogeheten patiënten gerapporteerde uitkomsten (PROMs) gekoppeld worden aan de klinische informatie. Alleen dan kan een volledig beeld ontstaan van de zorguitkomsten in de dagelijkse praktijk.

De gerandomiseerde onderzoeken van de nieuwe melanoom medicijnen tonen de uitkomsten van één te testen behandeling ten opzichte van een controlebehandeling, meestal de geldende gouden standaard. We weten echter uit de dagelijkse praktijk dat verschillende nieuwe medicijnen vaak opeenvolgend worden voorgeschreven. In **hoofdstuk 5** is onderzocht of melanoompatiënten met een agressieve ziekte baat hebben bij een behandeling met doelgerichte therapie in de vorm van BRAF-remming, al dan niet in combinatie met MEK-remming, voorafgaand aan een behandeling met immunotherapie. De gedachte is dat er door de zeer krachtige antitumor effecten van BRAF- en MEK-remmers snel maar tijdelijk resultaat geboekt kan worden, zodat er meer tijd zou zijn om van de effecten van immunotherapie te kunnen profiteren. Agressieve ziekte wordt in deze studie gedefinieerd als het hebben van een >2 keer verhoogd LDH gehalte. Ook al zijn de aantallen klein, de studie laat zien dat patiënten waarbij het LDH gehalte normaliseert tijdens de behandeling met BRAF-/MEK-remming een goede kans hebben op respons van immunotherapie. Daarnaast blijkt immunotherapie niet heilzaam bij patiënten waarbij het LDH gehalte verhoogd blijft. Ondanks het feit dat klinische trials nodig zijn om het effect van een bepaalde volgorde van behandelingen aan te tonen, kan deze informatie uit de DMTR van aanvullende waarde zijn.

De indicatie voor immunotherapie wordt nu uitgebreid naar andere vormen van kanker, zoals longkanker, nierkanker, hoofd-halstumoren, blaaskanker, Merkelcelcarcinoom en verschillende vormen van lymfomen. Als we de indicatiestelling voor longkanker als voorbeeld nemen, dan gaat het jaarlijks niet meer om een groep van 800 patiënten zoals bij het gemetastaseerd melanoom, maar om een groep van bijna 10.000 geschikte patiënten. Of de DMTR als blauwdruk kan fungeren voor andere registraties valt te bezien. Aan de ene kant hebben de eerste resultaten van de DMTR laten zien dat het zeer waardevolle informatie oplevert ten aanzien van kwaliteitsmeting van melanoomzorg in de dagelijkse praktijk. Echter, omdat de DMTR meerdere

doelen dient, is de registratielast aanzienlijk en de kosten die ermee gepaard gaan relatief hoog. Om een toekomstig register op te zetten, zal er moeten worden gekeken hoe de registratielast zoveel mogelijk kan worden beperkt. Dit kan worden opgelost door meerdere datasets te creëren voor de verschillende doelen: één kleine dataset met de meest belangrijke kwaliteitsdata, zoals casemixfactoren, het type behandeling, morbiditeit en mortaliteit, bestemd voor alle patiënten. Naast deze kern dataset zullen er additionele datasets worden toegevoegd, bestemd voor een kleinere steekproef voor bijvoorbeeld doelmatigheidsonderzoek.
Verder zou extractie van gegevens uit het elektronisch patiëntendossier (EPD) kunnen zorgen voor een sterke vermindering van de registratielast. Projecten zoals 'Registratie aan de Bron' hebben laten zien dat voor sommige DICA registraties alle items rechtstreeks uit het EPD kunnen worden gehaald.

Er moet wel gezegd worden dat de kosten voor de opzet en het onderhoud van een dergelijk kwaliteitsregister zoals de DMTR maar een fractie is van de totale kosten van de nieuwe geneesmiddelen. Het zorginstituut Nederland heeft uitgerekend dat er slechts 1% van de geneesmiddelenkosten per melanoom patiënt nodig zou zijn om de opzet en het onderhoud van de DMTR te kunnen bekostigen. Het is belangrijk dat de overheid, de zorgverzekeraars en de farmacotherapeutische bedrijven met elkaar in discussie gaan over de belangrijke vraag of het wenselijk is om een kleine bijdrage van het totale geneesmiddelenbudget uit te geven aan de kosten van toekomstige kwaliteitsregistraties.

Deel 3: kwaliteitsmeting met behulp van patiëntgerichte uitkomsten

Doordat de overleving van kankerpatiënten stijgt, worden traditionele uitkomstmaten zoals overleving en progressievrije ziekte, niet meer gezien als de enige uitkomsten die er toe doen, maar is het meten van patiënt gerapporteerde uitkomsten (PROMs) tijdens en na de behandeling veel belangrijker geworden. Daarnaast willen steeds meer patiënten in samenspraak met hun arts beslissen over de behandeling ('shared decision making'). Hiervoor is betrouwbare en voor de patiënt relevante uitkomstinformatie uit de dagelijkse praktijk essentieel. Ten slotte is het waardevol om informatie op een universele manier vast te leggen zodat het internationaal kan worden vergeleken.

ICHOM is een internationaal consortium voor uitkomstmetingen in de zorg, opgericht in 2012 door de Harvard Business School, de Boston Consulting Group en het Karolinksa Instituut. De missie van ICHOM is om voor de meest belangrijke ziektebeelden standaardsets van patiëntgerichte uitkomsten te definiëren die wereldwijd gebruikt kunnen worden.
Hoofdstuk 6 en **hoofdstuk 7** beschrijven het proces en het resultaat van twee werkgroepen die een ICHOM standaard set voor borstkanker en darmkanker hebben ontwikkeld.
De ICHOM sets werden ontwikkeld door een internationale werkgroep waarbij zorgverleners en patiënten samenwerkten. Met behulp van een systematische review van de literatuur en middels een Delphi proces werd er in acht maanden tijd een set met de belangrijkste patiëntgerichte uitkomsten gedefinieerd. De uitkomsten werden gevalideerd middels een patiënten survey en een panel van externe experts.
Beide sets omvatten veertien patiëntgerichte uitkomsten waarvan de meerderheid (70%) patiënt gerapporteerd zijn. De klinische uitkomsten hebben betrekking op de (ziekte vrije) overleving en ernstige complicaties. De patiënt gerapporteerde uitkomsten worden door middel van een aantal gevalideerde PROMS vragenlijsten uitgevraagd en hebben betrekking op de kwaliteit van leven van de patiënt, waarbij domeinen zoals emotioneel en cognitief functioneren worden vastgelegd alsmede symptomen zoals pijn, moeheid en lymfoedeem. Ten slotte worden er een aantal casemixfactoren geadviseerd, zoals patiënt- en tumorkarakteristieken en het type behandeling, om een zo eerlijke vergelijking mogelijk te maken.
DICA heeft recentelijk een deel van de borstkanker en de darmkanker ICHOM set geïntegreerd in de DICA audits, te weten de NABON Breast Cancer Audit (NBCA) en de Dutch ColoRectal Audit (DCRA).

Het gebruik van PROMs vragenlijsten voor kwaliteitsmeting staat nog steeds in de kinderschoenen. De PROMs vragenlijsten zijn vaak lange, statische vragenlijsten omdat ze speciaal ontwikkeld zijn voor wetenschappelijk onderzoek. De komende jaren zal er gekeken moeten worden hoe de vragenlijsten kunnen worden ingekort zonder dat ze waarde verliezen. Verder is uit onderzoek gebleken dat het erg belangrijk is om de PROMs uitkomsten niet alleen te gebruiken voor wetenschappelijk onderzoek of clinical auditing, maar ook in de spreekkamer. Als bijvoorbeeld blijkt uit de PROMs vragenlijsten dat een patiënt erg veel pijn heeft of depressieve klachten

aan het ontwikkelen is, kan daar in de spreekkamer gericht naar worden gekeken. Indien nodig kan een patiënt doorverwezen worden naar een andere zorgverlener. Het is daarnaast van belang dat de zorgverleners goed duidelijk maken aan de patiënt wat de meerwaarde is van de PROMs vragenlijsten.

Er zijn enkele kanttekeningen te plaatsen bij de manier waarop ICHOM zijn standaard sets vormgeeft. Het advies van ICHOM is om enkel de uitkomsten te registreren, waardoor er geen inzicht wordt verkregen in de processen die eraan ten grondslag liggen. Met behulp van het meten van zowel uitkomst- als procesindicatoren kan er gerichter een verbetertraject worden opgesteld.
Ook worden er geen adviezen gegeven ten aanzien van Patient Reported Experience Measures (PREMs) vragenlijsten. Bij PREMs gaat het om de ervaring en beleving van de patiënt. De resultaten kunnen waardevol zijn om zorg(processen) te verbeteren. Uit de patiënten survey van de borst- en darmkankerset van ICHOM bleek dat 20% van de deelnemers vond dat er PREMs vragenlijsten toegevoegd moesten worden.
Het meest waardevolle model is wellicht een hybride model waarbij zowel de belangrijkste procesindicatoren (klinisch en PREMs) als ook de belangrijke patiëntgerichte uitkomsten (klinisch en PROMs) worden vastgelegd.

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Curriculum vitae

List of publications

Dankwoord

CURRICULUM VITAE

Maartje Schouwenburg was born on the 8th of May 1987 in Leiden. After graduating cum laude from the Stedelijk Gymnasium in Leiden, she decided to study Medicine at the University of Utrecht in 2005.

After receiving her medical degree, she did a minor in Business and Entrepreneurship because of her interest in business, management and strategy; subjects she believed are increasingly important in the healthcare sector but are underrepresented at Medical School.
Through her work as an intern (ANIOS) at the department of general internal medicine at the Amstelland Ziekenhuis, she obtained clinical experience in a range of specialties including oncology, cardiology and gastroenterology.

The combined PhD program at the Dutch Institute for Clinical Auditing (DICA) and the Leiden University Medical Centre created an opportunity to combine her interest in research with developing her skills in management and organisation as a project manager of several clinical audits. She performed her research under the supervision of her promotor prof. dr. J.J.M. van der Hoeven and copromotores dr. M.W.J.M. Wouters and prof. dr. R.A.E.M. Tollenaar. She focused her research on assuring quality of cancer therapy with expensive anticancer drugs.
During her PhD time at DICA, she was given the opportunity to work as a project leader at the International Consortium for Health Outcomes Measurement (ICHOM) in Boston. During this project, she gained more insight into the added value of patient centred outcomes in addition to traditional outcomes in assuring quality for colorectal and breast cancer care.

Together with five other PhD students, she organized a two-day masterclass for young healthcare professionals with the aim of creating more awareness about value-based healthcare and to discuss different concepts on how to realize a more sustainable healthcare system in the future.

After her PhD program, she started her GP training program at the VU Medical Centre in Amsterdam in 2017. The diversity of patients, the variety in medical condi-

tions and the opportunity to build long lasting relationships with patients and their families were one of her main motives to become a GP.

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DANKWOORD

Dit proefschrift is mede tot stand gekomen dankzij het werk en de steun van velen. Ik wil iedereen hiervoor van harte bedanken en een aantal mensen in het bijzonder.

Mijn promotor prof. dr. ir. J.J.M. van der Hoeven. Beste Koos, ik heb bewondering voor jouw bijdrage aan de (maatschappelijke) discussie rondom de toegankelijkheid en bekostiging van dure geneesmiddelen. Je hebt me op een persoonlijke en inspirerende manier begeleidt en daarnaast verschafte je me de inzichten die ik nodig had om dit proefschrift tot een geheel te maken.

Mijn tweede promotor prof. dr. R.A.E.M. Tollenaar. Beste Rob, jouw visie op het gebied van kwaliteitsonderzoek tijdens de promovendi uurtjes was een bron van inspiratie. Onze intensieve samenwerking tijdens het ICHOM project heb ik als zeer leerzaam en plezierig ervaren.

Mijn copromotor dr. M.W.J.M. Wouters. Beste Michel, jouw uitgebreide kennis en ervaring op het gebied van kwaliteitsonderzoek en jouw enthousiasme werkt aanstekelijk en motiverend. Ik heb veel geleerd van onze inhoudelijke discussies.

De wetenschappelijke commissies van de DMTR en de DUCA, jullie kritische blik op mijn ideeën en artikelen heeft mij focus aangebracht tijdens dit promotietraject. Datamanagers van de DMTR, bedankt voor het zorgvuldig invoeren van alle data van deze zeer uitgebreide en complexe dataset.

Alle coauteurs en in het bijzonder Linde, Naomi, Michiel, Anouk, Annelotte, Brenda en Margreet, al het statistisch en inhoudelijk gepuzzel was een stuk moeilijker (en minder leuk) geweest zonder jullie hulp.

Dear Caleb, I am grateful for our collaboration during my ICHOM period. You were always helpful, friendly and supportive. Thank you for taking time for our weekly meetings out of your busy schedule, you've never skipped one.

Lieve C11, K3, C7 en collega's van het Poortgebouw, niet voor niets gaat de laatste stelling over jullie! Ook al was het soms pionieren bij DICA, door onze hechte band stonden we altijd voor elkaar klaar. Alle congressen, borrels, fietstochten en etentjes hebben ervoor gezorgd dat ik een onvergetelijke tijd heb gehad.

Lieve paranimfen, Charlotte en Naomi, jullie waren beiden een rots in de branding tijdens mijn gehele promotietraject.

Lieke, Linde, Annelotte en Pauline. Ik denk met een grote glimlach terug aan al die fantastische toertochten, Viking borrels en Ringvaart ritjes naar Leiden. Gelukkig staat de volgende fietstocht al op de planning!
Lieve Pauline, wat was het fijn om samen naar het einde toe te werken. Het was pittig, maar ook erg gezellig. En, gedeelde smart is halve smart!

Mijn lieve familie, in het bijzonder mijn ouders, Jeroen en Wilma, jullie waren altijd oprecht geïnteresseerd in mijn proefschrift en apetrots als er een artikel werd geaccepteerd voor publicatie. Dank voor jullie betrokkenheid.
Lieve vrienden, zonder ontspanning geen proefschrift!

Lieve Frank, bedankt voor je steun en rotsvaste vertrouwen in mij. Je bent er altijd voor me, jij maakt me gelukkig!