Clinical Usefulness of Tools to Support Decision-making for Palliative Treatment of Metastatic Colorectal Cancer: A Systematic Review

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Abstract

A systematic review of the literature was performed to provide a comprehensive overview of the available decision support tools for incurable metastatic colorectal cancer, and to assess their clinical usefulness. We identified 14 tools. The evidence regarding the quality of the information they provide is too limited to currently recommend their use to guide treatment decision-making.

Background: Decision-making regarding palliative treatment for patients with metastatic colorectal cancer (mCRC) is complex and comprises numerous decisions. Decision-making should be guided by the premise of maintaining and/or improving patients' quality of life, by patient preference, and by the trade-off between treatment benefits and harm. Decision support systems (DSSs) for clinicians (eg, nomograms) can assist in this process. The present systematic review aimed to provide a comprehensive overview of the available DSSs for incurable mCRC and to assess their clinical usefulness. **Materials and Methods:** A systematic literature search was performed in PubMed, Embase, and the Cochrane Library. We extracted information on the DSS characteristics and their discriminatory ability, calibration, and user-friendliness. **Results:** From 5205 studies, we identified 14 DSSs for decisions regarding palliative resection of the primary tumor (n = 3), radiotherapy for metastases (n = 2), treatment type (invasive vs. symptomatic only; n = 7), and selection of chemotherapy (n = 2). The predictors varied greatly among the DSSs, and only 1 DSS incorporated a genetic marker (ie, *UGT1A1*). None of the DSSs included > 1 treatment option, nor did any DSS present estimates of treatment benefits and harms. Five tools had not been externally validated, two had only been validated in < 35 patients, and the rest had only been validated in populations similar to the population used for their development. Discriminatory accuracy was generally moderate to poor. Calibration measures were only reported for 2 tools. **Conclusion:** A limited number of DSSs are available to support palliative treatment decisions for patients with mCRC, and the evidence regarding their discriminatory ability and calibration is too limited to recommend their use. New DSSs comparing multiple treatment options and presenting both treatment benefits and harms are needed.

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Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women. Worldwide, in 2012, 9% to 10% of all incident cancer cases in men and women were CRC. Approximately one quarter of CRC patients will have metastatic disease at diagnosis, and approximately 50% of CRC patients with early-stage disease will develop metastases during follow-up.[1] CRC mortality varies greatly by disease stage, with stage I patients having, on average, 5-year survival rates > 90% and those with metastatic disease 5-year survival rates of 10% to 20%.[2] However, great variation also exists in the survival among patients with metastatic CRC (mCRC), because some patients will still be eligible to undergo surgery with curative intent. For example, recent studies have reported 5-year survival rates of 25% to 40% for mCRC patients with resectable liver metastases.[1,3] Also, for those with successfully resected peritoneal metastases, 5-year survival rates of ≤ 50% have been reported.[3,4] However, most mCRC patients will have either permanently unresectable metastases or local recurrence and therefore will not be eligible to receive (further) curative treatment. In this population, treatment has a palliative intent. Palliative care, as defined by the World Health Organization, primarily aims to improve the quality of life of patients through the early identification, assessment, and treatment of physical, psychosocial, and spiritual issues.[5] Palliative care can consist of treatments directed at limiting tumor growth and associated symptoms (eg, pain) and treatments solely intended to relieve symptoms (ie, physical, emotional, and spiritual). Although cure is no longer possible, treatments directed at limiting tumor growth can prolong patients' life (which, in the case of mCRC, can result in a median overall survival benefit > 2 years). However, systemic treatments directed at limiting tumor growth are also associated with side effects that can affect patients' quality of life.

Decision-making about palliative care for CRC is complex and multifaceted. These decisions are often preference-sensitive (ie, no single choice is "best" from a medical perspective). It is imperative to find the right balance between maximizing length of life and optimizing quality of life to reach a decision that best matches the patient's goals and preferences. The complexity results in part from the many possible treatment combinations, and the heterogeneity of the patient population with respect to, for example, the location of the metastases and the resectability of the primary tumor. Decision support systems (DSSs), which generate case-specific treatment advice, can help oncologists to present the options to their patients and better weigh the trade-off between the benefits and harms of palliative treatment. DSSs would ideally compare multiple treatment options and predict the outcomes, such as survival and potential treatment gains in terms of survival, toxicity, and cost-effectiveness. Currently, a comprehensive overview of published DSSs to guide clinical decision-making about palliative treatment for incurable mCRC is lacking. Research has mainly focused on the development of tools to inform decision-making about treatments with curative intent (especially surgical treatment) and/or determining whether treatment with curative intent is still feasible for patients with mCRC. Furthermore, the available reviews of DSSs for treatment decision-making used a limited search strategy, only focused on 1 type of tool (eg, Kawai et al[6] focused on available nomograms to help CRC treatment decision-making), or only focused on 1 specific clinical decision (eg, Tokuhashi et al[7] focused on DSSs for treatment decision-making about spinal metastases). We, therefore, conducted a systematic search of published DSSs for decision-making about palliative treatment for patients with incurable CRC. We have provided an overview of the characteristics of the DSS (eg, purpose, predictors, and type of tool); level of evidence regarding the DSSs' discriminatory accuracy and calibration; and the user-friendliness of the DSSs.

Materials and Methods

Systematic Literature Search

In collaboration with an experienced information specialist (E.P.J.), a systematic literature search was performed to identify all relevant studies in the bibliographic databases PubMed, EMBASE, and the Cochrane Library (via Wiley) from inception to February 23, 2016. The search terms included controlled terms from MeSH in PubMed, EMtree in Embase, and free text terms only in the Cochrane Library. Search terms expressing "colorectal cancer" were combined with search terms comprising "decision support systems" and "prognosis" (the detailed search strategy is provided in Table 1). The references of the identified reports were searched for additional relevant studies. In addition to our search of the bibliographic databases, we searched the websites of the American Society of Clinical Oncology, National Institute for Health and Care Excellence, National Comprehensive Cancer Network, European Society for Medical Oncology, and the DSS indexing website (www.MedicalAlgorithms.com) for references to additional DSSs.

Selection Process

The aim of our search was to identify available complete DSSs (not individual predictors) to aid decision-making regarding palliative treatment for patients with incurable mCRC. Tools not specifically developed for decision-making for incurable mCRC that had been validated in this patient population were also eligible for inclusion. DSSs for decision-making regarding surgery, radiotherapy, and/or systemic therapy for incurable mCRC were eligible for inclusion. Also eligible were DSSs marking the transition from palliative care, including treatment directed at limiting tumor growth to noninvasive treatment for symptom relief only.

The titles and abstracts were screened by 3 of us (E.G.E., H.C.W.d.V., and J.J.T.) independently, and discrepancies were resolved through consensus. After the identification of potentially relevant studies, 1 of us (E.G.E.) made the final selection of DSSs by screening the full text reports; when in doubt, 3 of us (H.C.W.d.V., J.J.T., and V.M.H.C.) were consulted. Because the aim of the present study was to assess the usefulness of available tools in current clinical practice, DSSs only developed and/or validated in patient populations not treated according to current guidelines and those predicting prognosis with treatments no longer in use were excluded. To ensure that the information derived from the development and validation studies assessed in the present review is relevant for current clinical practice, we applied time restrictions

Table 1 Detailed Search Strategy for Each Database

Database	Search Terms
PubMed	"Colonic neoplasms" [MeSH] OR "colorectal neoplasms" [MeSH] OR colonic neoplasm*[tiab] OR colon neoplasm*[tiab] OR "cancer of colon"[tiab] OR "cancer of the colon"[tiab] OR colon cancer*[tiab] OR colonic cancer*[tiab] OR colorectal neoplasms*[tiab] OR colorectal tumor*[tiab] OR colorectal tumour*[tiab] OR colorectal carcinoma*[tiab] OR colorectal cancer*[tiab] AND "decision support systems, clinical" [MeSH] OR "decision support techniques" [MeSH] OR "nomograms" [MeSH] OR "Markov chains" [MeSH] OR decision support system*[tiab] OR decision support technique*[tiab] OR decision aid*[tiab] OR decision support model*[tiab] OR decision analys*[tiab] OR decision modeling[tiab] OR nomogram*[tiab] OR prediction rule*[tiab] OR (prognos*[tiab] AND (index[tiab] OR score*[tiab] OR model*[tiab])) OR markov[tiab] AND ("prognosis" [MeSH:noexp] OR "incidence" [MeSH Terms:noexp] OR mortality [MeSH terms] OR follow up studies [MeSH:noexp] OR prognos*[tiab] OR predict*[tiab] OR course*[tiab] OR mortalit*[tiab]) OR "life expectancy"[MeSH] OR "survival rate"[MeSH] OR "longevity"[MeSH] OR "longevity"[tiab] OR "life expectancy" [tiab] OR "life expectance"[tiab] OR "life expectation"[tiab] OR "survival"[tiab] OR prognos*[tiab] OR (toxicit*[tiab] OR toxic potential*[tiab] OR "margin of safety"[tiab] OR adverse effect*[tiab] OR survival[tiab])
Embase	"colon tumor"/exp OR "colorectal tumor"/exp OR "colonic neoplasm*":ab,ti OR "colon neoplasm*":ab,ti OR "cancer of colon":ab,ti OR "cancer of the colon":ab,ti OR "colon cancer*":ab,ti OR "colonic cancer*":ab,ti OR "colorectal neoplasms*":ab,ti OR "colorectal tumor*":ab,ti OR "colorectal tumour*":ab,ti OR "colorectal carcinoma*":ab,ti OR "colorectal cancer*":ab,ti AND "decision support system"/exp OR "nomogram"/exp OR "probability"/exp OR "decision support system*":ab,ti OR "decision support technique*":ab,ti OR "decision aid*":ab,ti OR "decision support model*":ab,ti OR "decision analys*":ab,ti OR decision AND modeling:ab,ti OR "prediction rule*":ab,ti OR probabilit*:ab,ti OR nomogram*:ab,ti OR (prognos*:ab,ti AND (index:ab,ti OR score*:ab,ti OR model*:ab,ti)) OR markov:ab,ti AND "prognosis"/exp OR "incidence"/exp OR "mortality"/exp OR "follow up"/exp OR predict*:ab,ti OR course*:ab,ti OR mortalit*:ab,ti OR "life expectancy"/exp OR "survival rate"/exp OR "longevity"/exp OR "longevity":ab,ti OR "life expectancy":ab,ti OR "life expectance":ab,ti OR "life expectation":ab,ti OR "survival":ab,ti OR prognos*:ab,ti OR toxicit*:ab,ti OR "toxic potential*":ab,ti OR "margin of safety":ab,ti OR "adverse effect*":ab,ti AND ("article"/it OR "article in press"/it OR "review"/it)
Cochrane Library	"Incidence" OR mortality OR follow up studies OR prognos* OR predict* OR course* OR mortalit* OR "life expectancy" OR "longevity" OR "life expectancy" OR "life expectance" OR "life expectation" OR "survival" OR toxicit* OR toxic potential* OR "margin of safety" OR adverse effect* OR survival:ti,ab,kw AND "decision support system*" OR "decision support technique*" OR "decision aid*" OR "decision support model*" OR "decision analys*" OR "decision modeling OR prediction rule*" OR nomogram* OR (prognos* and (index or score* or model*)) or markov:ti,ab,kw AND "colonic neoplasm*" OR "colon neoplasm*" OR "cancer of colon" OR "cancer of the colon" OR "colon cancer*" OR "colonic cancer*" OR "colorectal neoplasms*" OR "colorectal tumor*" OR "colorectal tumour*" OR "colorectal carcinoma*" OR "colorectal cancer*":ti,ab,kw

(Table 2) using the last major changes in treatment advice introduced in the 2014 Dutch treatment guidelines,[8] which roughly coincided with international guidelines (eg, European Society for Medical Oncology guidelines[9]).

Search for Additional Studies

After the final selection of DSS, a manual search was performed for each DSS to identify reports describing its development, validation, and/or any updates. Reviews found using the search strategy and the "cited by" function in PubMed were used to find additional studies. We also performed a manual search in PubMed to identify validation studies for each DSS using the following terms: (name of the DSS) AND (terms for colorectal cancer [Table 1]) AND (validat*). One of us (E.G.E.) screened all identified additional reports and made the final selection. Doubts regarding the selection of studies were resolved through consensus (H.C.W.d.V., J.J.T., V.M.H.C.).

Data Extraction

An overview of the data extracted from the full text reports is provided in Table 3. Model performance assessment was determined by the findings of the validations and described using measures for discriminative ability (eg, C-index). The methods used to determine model calibration were classified using the levels described by Van Calster et al.[11] The level of evidence for the discriminatory accuracy and calibration of the DSSs is described using the levels of evidence reported by Reilly and Evans.[12] Evaluation of the user-friendliness of the DSS was based on whether the predictors were routinely collected, ease of use (eg, availability of a nomogram or online tool), and accessibility (eg, freely accessible or access by subscription only). Data extraction was performed by 1 of us (E.G.E.), with 3 of us (H.C.W.d.V., J.J.T., V.M.H.C.) consulted when in doubt.

Results

The literature search yielded 5205 unique reports, from which we identified 14 DSSs developed to aid treatment decision-making for patients with incurable mCRC (Figure 1). No additional references were found from the websites of the professional groups. A graphic overview of the DSSs identified is shown in Figure 2, categorized by the type of treatment and their purpose.

DSS Characteristics

A detailed overview of the characteristics of the DSSs, including their development, output, validation, and user-friendliness, is provided in Table 4. We identified 10 prognostic scores,[13-15,17-20,22-24] 3 nomograms,[16,21,25] and 1 chemotherapy sensitivity and resistance assay.[26] Of the 14 tools,

Table 2 Time Restrictions for Data Search[a]

Outcome	Cutoff Diagnosis Year[b]
Prognosis in general	≥2006
Prognosis postoperatively (colon cancer)	≥1985
Prognosis postoperatively (rectal cancer)	≥2001
Selection of patients for palliative resection of primary tumor in presence of unresectable metastases	≥2006
Prognosis with and without radiotherapy	≥1985
Prognosis with and without systemic therapy	≥2006
Risk of developing side effects	≥2006
Selection of optimal treatment strategy	≥2006

[a]Decision support systems were eligible for inclusion if they were developed and/or validated in patients with colorectal cancer diagnosis.
[b]Cutoffs were determined by when the last major changes in treatment advice were introduced in the Dutch treatment guidelines (which roughly coincided with international guidelines).

Table 3 Data Extraction From Included Reports

Category	Description of Items
Development population	Description of the study population
	Number of patients in the population
	Years of diagnosis of the study population
	Setting
	Study design
Aim	Purpose of DSS as stated by developers
Predictors	Predictors included in DSS
Output	Is the model presented as a nomogram
	If presented as risk categories, how many were included
	Description of prognostic categories
	Prognosis for patients in the risk categories
Validation population	Description of the study population
	Number of patients
	Years of diagnosis for the study population
	Setting
	Study design
Model performance	
Discriminative ability	A measure for the extent to which the DSS is able to discriminate between 2 outcomes or conditions (eg, death vs. alive); findings from external validations (if available) are described; if included in the study, the area under the curve or C-statistics is reported; interpretation of C-index: <0.6, poor; 0.6-0.7, moderate; 0.7-0.8, strong; >0.8, very strong[10]
van Calster levels of calibration[11]	These levels indicate the methodologic soundness of the method used to determine model calibration: 1. Mean calibration method: comparison of average predicted risk to average observed risk 2. Weak calibration method: assessment of the presence of systematic over- or underfitting using regression analyses 3. Moderate calibration method: comparison between deciles of predicted and observed outcomes 4. Strong calibration method: comparison of event rate to predicted risk for all possible combinations of covariates
Reilly levels of evidence[12]	Measure for how thoroughly the DSS is validated: Level 1: derivation from a prediction model and not yet externally validated Level 2: narrow validation in one setting Level 3: broad validation in varied settings and populations Level 4: narrow impact analysis of model as decision rule in one setting Level 5: broad impact analysis of model as decision rule in varied settings and populations
User-friendliness	
Predictors routinely collected	Are the predictors in the DSS routinely collected in clinical practice
Ease of use	Is it easy to apply the tool (eg, scoring system is easily derived from the report)
Online tool available	Is an online tool available

Abbreviation: DSS = decision support system.

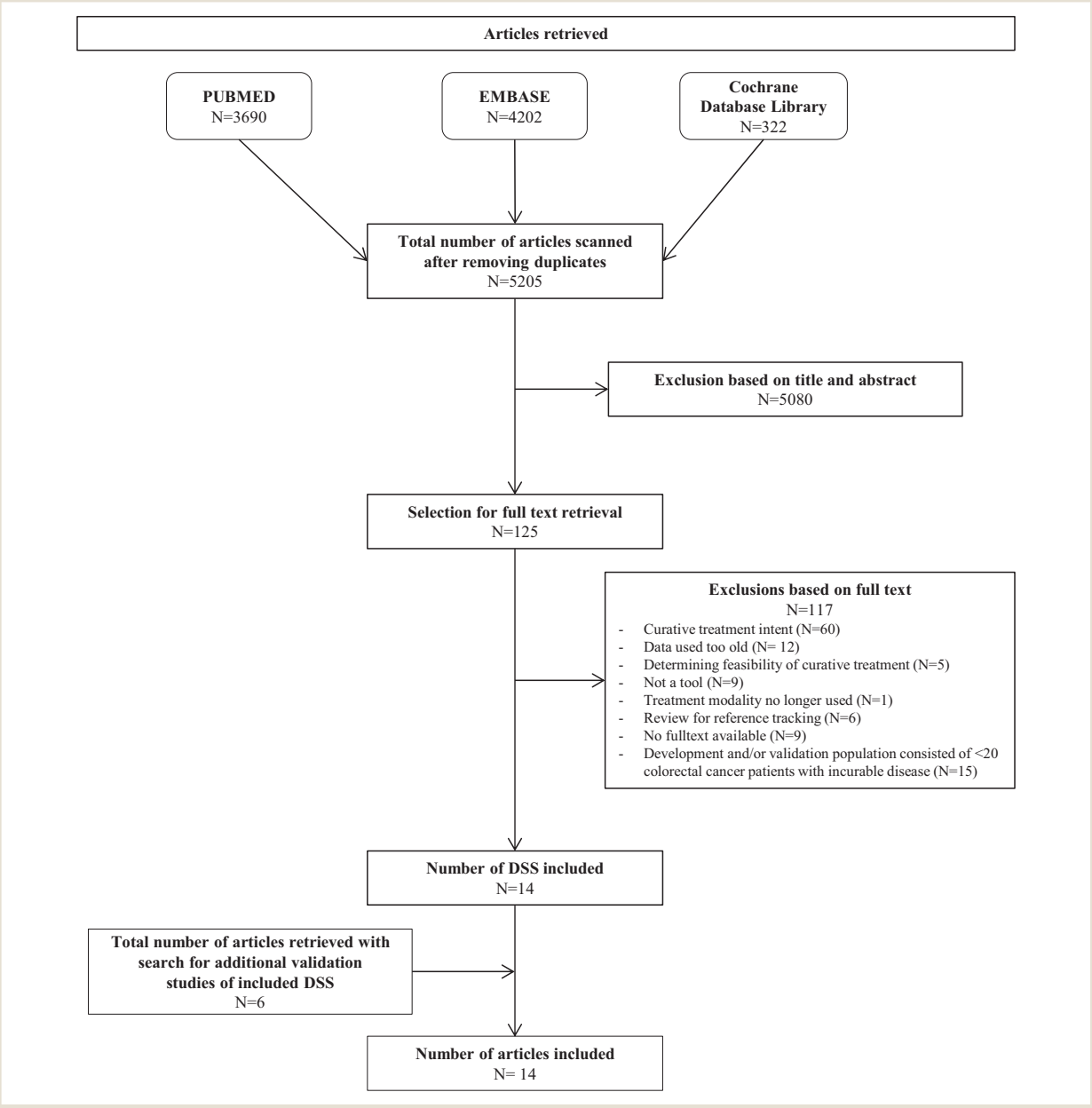
10 were developed in the previous 5 years (ie, after 2011). Six of the DSSs had focused on patients with either brain or skeletal metastases.[17-22] Eight of the DSSs identified were developed and/or only validated in Asian[13-15,25] or European populations.[16,20,21,26] Furthermore, great variation was found in the factors included in the DSSs. Only 3 factors were incorporated in > 2 DSSs (ie, patient age, performance status, and distant metastasis location; Figure 3). The variation in predictors among the DSSs was not fully explained by the DSSs having different aims or because they focused on specific subgroups of incurable mCRC patients (Table 4).

The DSSs we identified only focused on one side of the trade-off involved in decision-making—predominantly, the benefits of treatment (n = 10). None presented information on the expected treatment benefit and risks of side effects or, for example, the expected quality adjusted life expectancy. Also, none of the DSSs compared different treatment options. Five of the DSS aimed to help oncologists decide whether one specific treatment would be worthwhile, given the patients' expected survival period.[13-16,22] Seven other DSSs aimed to inform oncologists' evaluation regarding whether it would be worthwhile to pursue invasive treatment options in general, given the patients' prognosis.[17-21,23,24] One DSS aimed to help oncologists select the most effective chemotherapy regimen.[26] Finally, 1 DSS aimed to help oncologists select patients likely to develop a severe side effect a priori to take preventive measures.[25]

Level of Evidence for DSSs

Generally, the tools were developed and validated in non-randomized populations of patients that had received the same

Figure 1 Flowchart of Systematic Literature Search and Article Selection

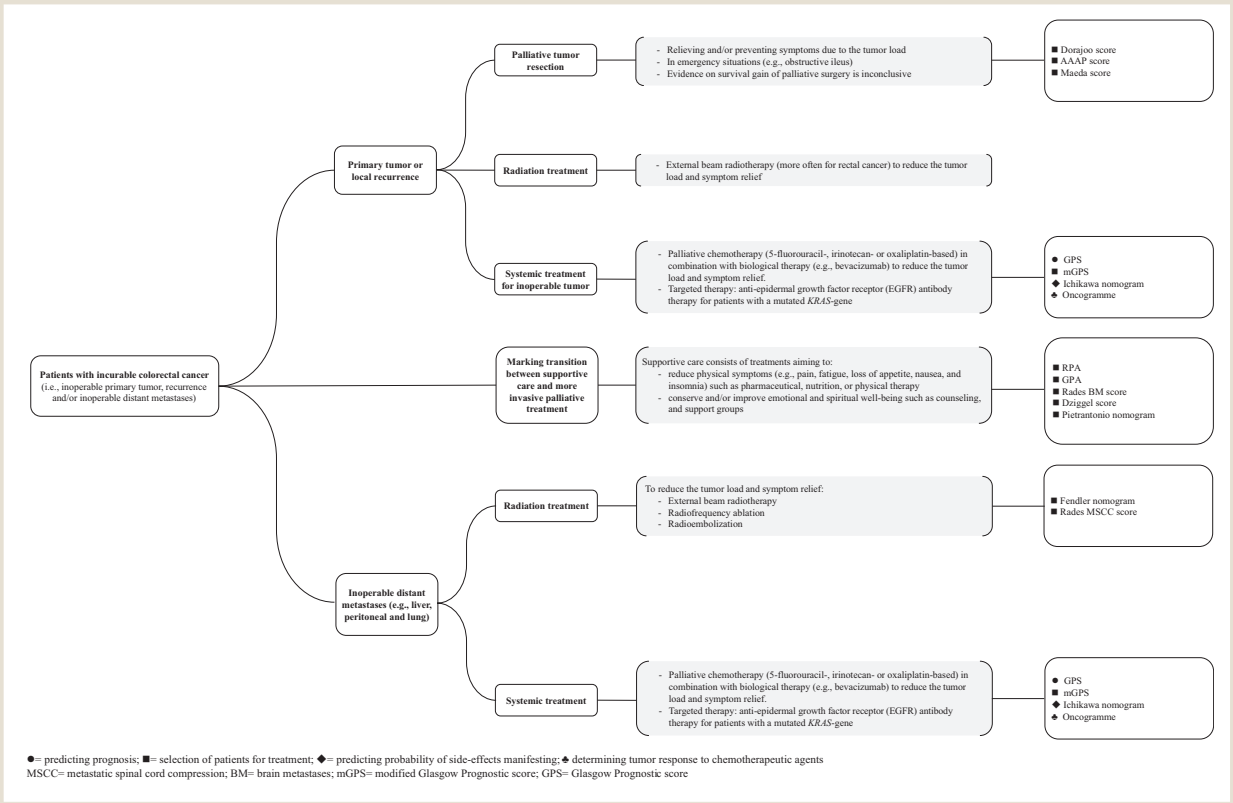


Abbreviation: DSS = decision support system.

treatment. Only 1 study had included a control group.[26] Of the 14 DSSs identified, 5 were not externally validated. Calibration measures were only reported in 2 validation studies.[21,25] We did not identify any impact studies for any of the DSSs included. Of the 14 DSSs, 9 only achieved the lowest level of evidence (ie, Reilly level 1). The other 5 DSSs reached a Reilly level of evidence of 2 (Table 4). In the next sections, we describe the DSSs identified according to their purpose and present the available data regarding the level of evidence.

DSS Predicting Prognosis in General. The Glasgow Prognostic Score (GPS) was developed using a cohort of incurable lung cancer patients to predict the prognosis in general (Table 4).[23] We found many studies in which the GPS was evaluated, including studies of incurable metastasized CRC. Most of these studies aimed to evaluate whether the GPS is a predictor of survival that could be incorporated into a DSS, not whether it can be used as a DSS on its own. Also, the data used in a number of studies was too old. Therefore, only the study by Maillet et al[28] met our inclusion criteria. Their study showed that the GPS is an independent prognostic tool in a population of incurable CRC patients treated with chemotherapy and bevacizumab.[28] In the multivariate analysis, only GPS remained as a significant factor. The GPS was reported to

Figure 2 Overview of Published Tools to Aid Palliative Treatment Decisions for Patients With Incurable Colorectal Cancer



discriminate among patients with good, moderate, and poor prognosis (Table 4). However, the methods used to determine the GPS' discriminatory accuracy were not optimal, and model calibration was not assessed.

DSS Selecting Patients for Whom Treatment Could Be Worthwhile. Fendler et al[16] developed a nomogram to predict the probability of 1-year survival for CRC patients with inoperable liver metastases after treatment with selective internal radiation therapy (Table 4). Currently, little can be reported about the performance of this nomogram, because the validation population consisted of only 25 patients.[16]

Three of the DSSs aimed to aid decision-making regarding elective resection of the primary tumor if the patients have unresectable distant metastases, the AAAP (ie, age, alkaline phosphatase, ascites, platelet/lymphocyte ratio) score,[13] the score by Dorajoo et al,[14] and the score by Maeda et al.[15] Although developed to support the same decision, different predictors were incorporated into these tools, and they predicted different outcomes (Table 4). For example, the AAAP score predicts the probability of 2-year overall survival, and the Dorajoo score predicts cancer-specific survival. All 3 tools were developed in Asian patient populations. Only the Dorajoo score was externally validated, although also in an Asian population. The concordance probability estimate in the validation study was 0.65 and the time-dependent discriminatory accuracies ranged from 0.70 to 0.75 (Table 4). No calibration measures were reported for the Dorajoo score.[14] No consensus has been reached on whether resection of the primary tumor yields a survival benefit for patients with unresectable metastases, although a recent study has shown that that might be the case.[30]

McMillan et al[24] developed a modified version of the GPS (mGPS; Table 4), which has also been evaluated in numerous studies. Except for 1 study,[29] all were excluded because they assessed whether the mGPS was a potentially relevant component of a DSS and not whether it was an independent tool. Ishizuka et al[29] investigated the prognostic value of the mGPS in a population of CRC patients with an unresectable primary tumor and/or unresectable metastases undergoing palliative chemotherapy (Table 4). In the multivariate analysis, only mGPS remained as a significant factor and seemed to be able to discriminate among the 3 prognostic categories (Table 4). However, the Kaplan-Meier survival curves for the mGPS score 0 and 1 categories overlapped, suggesting that reevaluation of the cutoffs used in the scoring system might be required. The methods used to assess the mGPS' discriminatory accuracy were not optimal, and its calibration was not assessed.

We included tools developed to select patients with incurable mCRC who would be likely to benefit most from more invasive treatment of brain metastases. These included recursive partitioning analysis (RPA),[17] the graded prognostic assessment (GPA),[18] the nomogram by Pietrantonio et al,[21] the score by Dziggel et al,[19] and the score by Rades et al[20] (Table 4).

Table 4 Detailed Overview of Characteristics, Purpose, Output, and Performance of Decision Support Tools Identified

Variable	Name of Tool (Publication Date)											
	AAAP Score[13] (2015)	Dorajoo Score[14] (2015)	Maeda Score[15] (2013)	Fendler Nomogram[16] (2015)	RPA,[17] GPA[18] (1997, 2008)	Dziggel Score[19] (2014)	Rades BM Score[20] (2015)	Pietrantonio Nomogram[21] (2015)	Rades MSCC Score[22] (2012)	GPS,[23] mGPS[24] (2003, 2007)	Ichikawa Nomogram[25] (2015)	Oncogramme[26] (2016)
Development population												
Population	CRC, SYN, UR Met, ER of PT	CRC, UR Met, elective resection of PT	CRC, ASX PT, UR Met	CRC, UR liver Met refractory to CTx	Cancer with BM[a]	Cancer with BMs from less RS tumors treated with WBRT	CRC 3 BM_{max} after STS	CRC, SYN or MC BM	CRC, impaired motor function from MSCC, RT	UR lung cancer[a]	Advanced CRC, irinotecan-containing CTx	Stage IV CRC (curable and incurable), 5-FU, FOLFOX or FOLFIRI
Patients (n)	110	379	94	100	1200 (CRC not known)	34 CRC	19	227	121	161	1312	19
Years of diagnosis	2003-2012	1999-2005	2001-2009	2003-2010	1979-1993	NR	2000-2014	2000-2013	NR	1997-2002	2009-2012	2011-2012
Setting	1 Hospital, China	1 Hospital, Singapore	1 Hospital, Japan	1 Hospital, Germany	3 Clinical trials (RTOG 79-16, RTOG 85-28, RTOG 89-05)	NR	2 Hospitals, Germany	8 Hospitals, Italy	NR	1 Hospital, UK	299 Institutions, Japan	1 Hospital, France
Study design	Retro	Retro	Retro	Retro	Retro	Retro	Retro	Retro	Retro	Retro	Prosp, Observ	Prosp, PoC
DSS purpose												
Predicted outcome	2-y OS	CSS	OS	1-y OS	OS	6-mo OS	6- and 12-mo OS	OS	6-mo OS	OS	Probability of severe neutropenia (cycle 1)	Chemotherapy sensitivity and resistance
Treatment decision	Whether to perform ER of PT	Whether to perform ER of PT	Whether or to perform ER of PT	Whether to perform SIRT	Selecting optimal treatment strategy (invasive vs. BSC)	Selecting optimal treatment strategy (invasive vs. BSC)	Whether to perform follow-up treatment; which is best	Selecting optimal treatment strategy (invasive vs. BSC)	Whether to use RT	Not treatment-specific; prediction of prognosis to guide general treatment decisions	Choice of chemotherapy regimen; adjustment of doses	Choice of most effective treatment
Predictors	Age; ALP, ascites, PLR	Age, albumin, CEA, distant Met location, histologic tumor grade	PS, GPS, NLR, Met extent	Previous liver surgery, CEA, transaminase, diameter of 2 largest Met	EC Met, KPS, age, no. of BMs[a], no PD of PT[b,c], GPA, RPA[c]	Age, KPS, EC Met	EC Met, KPS, interval from BM diagnosis and STS	Age, KPS, BM location, BM no.	ECOG PS, visceral Met, mobility level before RT, timing of motor function impairment	CRP, albumin	Mono or combination CTx, initial irinotecan dose, age, sex, *UGT1A1* genotype, ECOG PS, bilirubin, ANC	NA, tumor tissue exposed to CTx
Output												
Prognostic categories	3	3	3	NA	RPA: 3 GPA: 4	3	4	NA	4	GPS/mGPS: 3	NA	NA
Description	Risk of death: low, 0 risk factors; moderate, 1- 2; high, 3-4 factors	Prognosis: good, 0-3 score; moderate, 4- 7; poor, >7 score	Risk of death: low, 0 risk factors; moderate: 1- 2; high, 3-4 factors	NA	RPA: class I, only good prognostic factors; class II, other patient; class III, KPS <70 GPA: class I, good; class II, intermediate to good; class III, intermediate to poor; class IV, poor	Prognosis: poor: 5-8 score; moderate, 9-11 score; good: >11 score	Prognosis: poor, score 0; moderate to poor, score 1; moderate to good, score 2; good, score 3	NA	Prognosis: poor: 8-12 score; moderate to poor, 13-18 score; moderate to good, 20-23 score; good, 24-27 score	Score 0, no risk factors; score 1, 1 risk factor; score 2, 2 risk factors (mGPS score of 1 only if CRP is elevated)	NA	NA

Table 4 Continued

Variable	Name of Tool (Publication Date)											
	AAAP Score[13] (2015)	Dorajoo Score[14] (2015)	Maeda Score[15] (2013)	Fendler Nomogram[16] (2015)	RPA,[17] GPA[18] (1997, 2008)	Dziggel Score[19] (2014)	Rades BM Score[20] (2015)	Pietrantonio Nomogram[21] (2015)	Rades MSCC Score[22] (2012)	GPS,[23] mGPS[24] (2003, 2007)	Ichikawa Nomogram[25] (2015)	Oncogramme[26] (2016)
Prognosis per category (survival in development study)	Median 2-y OS probability: low risk, 57%; moderate risk, 11%; high risk, 0%	Median CSS: good, 18 mo; moderate, 12 mo; poor, 5 mo	Median OS: low risk, 37 mo; moderate risk, 22 mo; high risk, 5 mo	NA	RPA 6- and 12-mo OS[d]: class I, 0%; class II, 51% and 29%; class III, 22% and 9% GPA 6- and 12-mo OS[d]: class I, 0%; class II, 0%; class III, 55% and 30%; class IV, 24% and 12%	Median 6-mo OS probability: poor, 11%; moderate, 38%; good, 83%	6- and 12-mo OS probability: poor, 17% and 0%; moderate to poor, 25% and 0%; moderate to good, 67% and 33%; good, 100% and 67%	NA	6-mo OS probability: poor, 0%; moderate to poor, 26%; moderate to good, 62%; good, 100%	GPS OS: score 0, 20 mo; score 1, 11 mo; score 2, 7 mo mGPS CSS: score 0, 454 days; score 1, 504 days; score 2, 253 days	NA	NA
Validation population and model performance												
Validation of included studies	0	1[14]	0	1[16]	1[21]	1[19]	0	2[21,27]	0	2[28,29]	1[25]	0
Population	NA	CRC, UR Met, ER of PT	NA	CRC, UR liver Met refractory to CTx	CRC, SYN or MC BM	Cancer patients with BM from less RS tumors treated with WBRT	NA	CRC, SYN or MC BM[21,27]	NA	GPS: CRC treated with 5-FU–based CTx and Bev[28]; mGPS: incurable CRC treated with CTx[29]	Advanced CRC treated with irinotecan-containing CTx	NA
Patients (n)	NA	103	NA	25	227	32 CRC patients	NA	119[21]; 64[27]	NA	GPS, 80; mGPS, 112	350	NA
Years of diagnosis	NA	2006-2007	NA	2008-2011	2000-2013	NR	NA	2005-2013[27]; NR[21]	NA	GPS: 2005-2012; mGPS, 2005-2007	NR	NA
Setting	NA	1 Hospital, Singapore	NA	1 Hospital, Germany	8 Hospitals, Italy	NR	NA	4 Italian,[21] 1 Norwegian,[27] 1 German[27] hospital	NA	NR	6 institutions, Japan	NA
Study design	NA	Retro	NA	Retro	Retro	Retro	NA	Retro[21,27]	NA	Retro	Prosp, Observ	NA
Discriminatory accuracy	NA	Concordance probability estimate, 0.65; AUC for 6, 12, 18, 24 mo CSS, 0.75; 0.73; 0.71; 0.70	NA	C-index, 0.83 (95% CI, 0.62-1.05)	C-index: RPA, 0.61; GPA, 0.59	6-mo OS differed among 3 prognostic categories (log-rank test; $P = .003$)	NA	C-index, 0.73[21]	NA	GPS/mGPS: prognosis differed between prognostic categories ($P < .05$)	C-index, 0.70	NA
Van Calster level of calibration[b]	NA	No calibration measures reported	NA	No calibration measures reported	No calibration measures reported	No calibration measures reported	NA	Moderate[21]	NA	No calibration measures reported	Weak	NA
Reilly level of evidence[c]	1	2	1	1	RPA: 2; GPA: 2	1	1	2	1	GPS: 1; mGPS: 1	2	1
User-friendliness												
Predictors routinely collected	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not *UGT1A1*	No, test kit must be purchased

Table 4 Continued

Variable	Name of Tool (Publication Date)											
	AAAP Score[13] (2015)	Dorajoo Score[14] (2015)	Maeda Score[15] (2013)	Fendler Nomogram[16] (2015)	RPA,[17] GPA[18] (1997, 2008)	Dziggel Score[19] (2014)	Rades BM Score[20] (2015)	Pietrantonio Nomogram[21] (2015)	Rades MSCC Score[22] (2012)	GPS,[23] mGPS[24] (2003, 2007)	Ichikawa Nomogram[25] (2015)	Oncogramme[26] (2016)
Ease of use	Moderate, not easy to derive from report	Good, can be derived from report	Good, can be derived from report	Good, can be derived from report	Good, can be derived from report	Moderate, not easy to derive from report	Moderate, not easy to derive from report	Good, can be derived from report	Moderate, not easy to derive from report	Good, can be derived from report	Good, can be derived from report	Manufacturer performs test
Online tool available	No	No	No	No	No	No	No	No	No	No	No	NA

Abbreviations: AAAP = age, ALP, and platelet/lymphocyte ratio; ALP = alkaline phosphatase; ANC = absolute neutrophil count; ASX = asymptomatic; AUC = area under the curve; Bev = bevacizumab; BM = brain metastasis; BM_{max} = maximum brain metastasis; BSC = best supportive care; CEA = carcinoembryonic antigen; CI = confidence interval; CRC = colorectal cancer; CRP = C-reactive protein; CSS = cancer-specific survival; CTx = chemotherapy; DSSs = decision support systems; EC = extracranial; ECOG = Eastern Cooperative Oncology Group; ER = elective resection; FOLFIRI = folinic acid, 5-fluorouracil, irinotecan; FOLFOX = folinic acid, 5-fluorouracil, oxaliplatin; 5-FU = 5-fluorouracil; GPA = graded prognostic assessment; GPS = Glasgow prognostic score; KPS = Karnofsky performance score; MC = metachronous; Met = metastases; mGPS = modified Glasgow prognostic score; MSCC = metastatic spinal cord compression; NLR = neutrophil/lymphocyte ratio; NR = not reported or unclear; Observ = observational; OS = overall survival; PLR = platelet/lymphocyte ratio; PoC = proof of concept; Prosp = prospective; PS = performance status; PT = primary tumor; Retro = retrospective; RPA = recursive partitioning analysis; RS = radiosensitive; RT = radiotherapy; SIRT = selective internal radiotherapy; STS = stereotactic surgery; SYN = synchronous; UR = unresectable; WBRT = whole brain radiotherapy.

[a]If DSSs were "related" (eg, RPA and GPA; GPS and mGPS), only the development population for the original DSS was described.

[b]Van Calster level of calibration: level 1, mean calibration method (comparison of average predicted risk to average observed risk); level 2, weak calibration (assessment of the presence of systematic over- or underfitting using regression analyses); level 3, moderate calibration (comparison between deciles of predicted and observed outcome); level 4, strong calibration (comparison of event rate to predicted risk for all possible combinations of covariates).

[c]Reilly level of evidence: level 1, derivation from a prediction model and not yet externally validated; level 2, narrow validation in 1 setting; level 3, broad validation in varied settings and populations; level 4, narrow impact analysis of model as decision rule in 1 setting; level 5, broad impact analysis of model as decision rule in varied settings and populations.

[d]Percentage of validation population.

The RPA and GPA have been validated in a large number of studies. However, except for the study by Pietrantonio et al,[21] small numbers (generally < 20) of incurable mCRC patients were included the validation cohorts. Also, only the tools' performance in the whole cohort was reported, not specifically their performance in incurable metastasized CRC patients. Brain metastases are not frequently observed in CRC patients, and they might respond differently to treatment than brain metastases from other primary tumor locations. Pietrantonio et al[21] reported poor to moderate discriminatory accuracy for the RPA and GPA (C-index for RPA, 0.59 and for GPA, 0.61), and their calibration was not reported (Table 4).

Simultaneously, Pietrantonio et al[21] also reported on the development and validation of a new nomogram that predicts the median overall survival for CRC patients with brain metastases. This tool aids oncologists in determining which patients will benefit most from invasive treatment directed at limiting tumor growth, combined with symptom relief, and which patients will be best served with less-invasive treatments (eg, symptom relief only). The discriminatory accuracy of this nomogram in the Italian external validation population was good (Harrels' C-index, 0.73); however, the calibration plot showed that the congruence between the predicted and observed survival was generally poor.[21] An external validation study using a cohort of Norwegian and German patients also found that the model calibration was poor.[27] It underestimated the survival of patients treated with stereotactic surgery by a median of 4.2 months and overestimated survival for those who had undergone whole brain radiotherapy by a median of 2.1 months.[27]

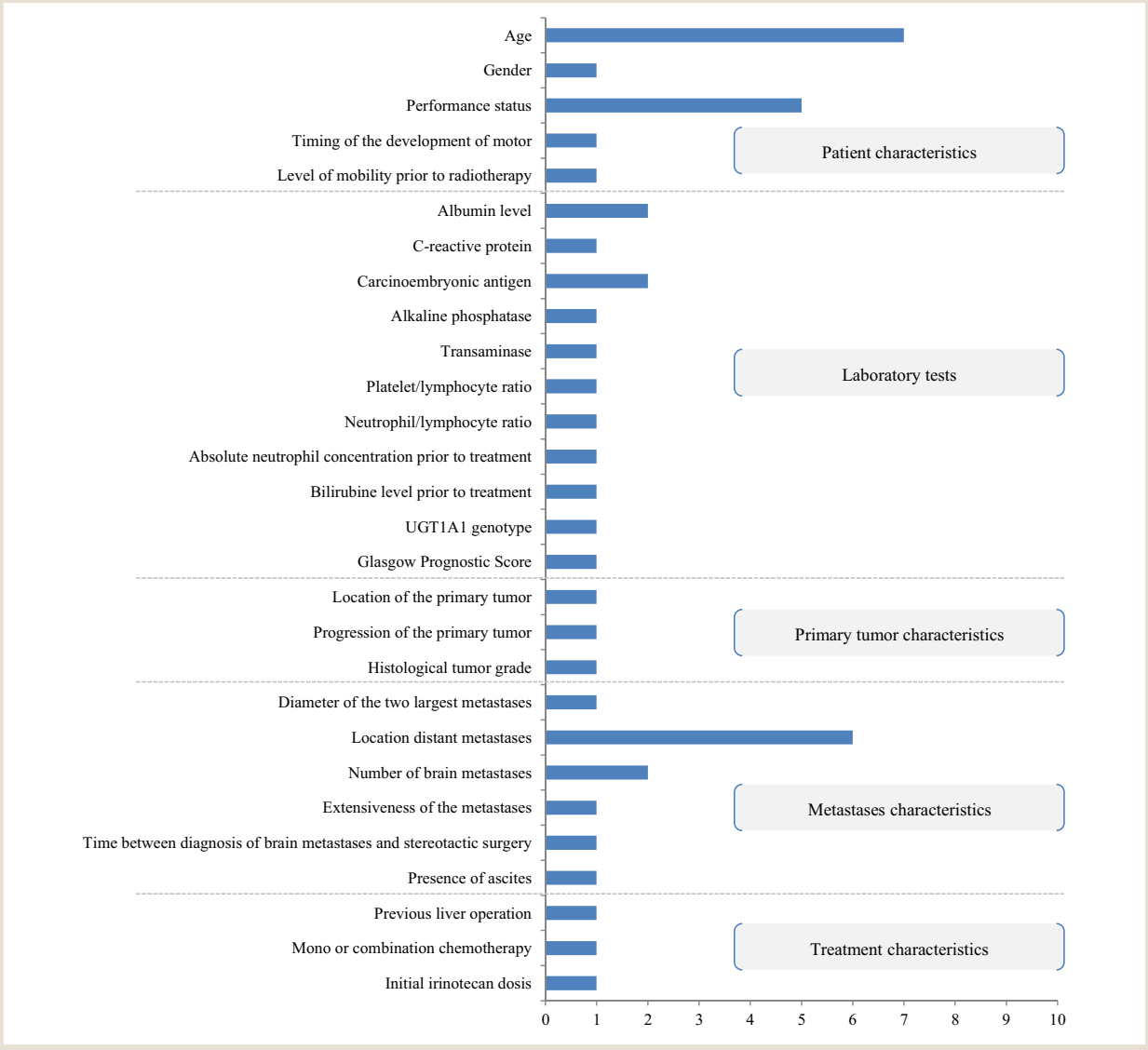
Dziggel et al[19] developed a prognostic score to aid treatment decision-making for patients with brain metastases from less-radiosensitive primary tumors (Table 4). This prognostic score was developed (n = 34) and validated (n = 32) in small samples of CRC patients. The methods used to determine discriminatory accuracy were poor, and calibration was not reported for this DSS.

Rades et al[20] developed a tool to aid in the selection of CRC patients with brain metastases who could benefit from stereotactic surgery. This tool was developed in a cohort of only 19 patients and has not been externally validated (Table 4). Rades et al[22] also developed a tool to aid in palliative radiotherapy decision-making for CRC patients with spinal cord compression due to spinal metastases (n = 121); that DSS also has not been externally validated.

DSS Predicting the Risk of Side Effects. Ichikawa et al[25] developed a nomogram to predict the probability of severe neutropenia during the first cycle of treatment with irinotecan for incurable mCRC patients (Table 4). This nomogram was developed and validated in Japanese patients, and the discriminatory accuracy was a C-index of 0.70. Calibration was good in the development population (n = 1312), but was not reported in the validation population (n = 350).

DSS Predicting Response to Systemic Treatment. Recently, a chemotherapy sensitivity and resistance assay,[26] Oncogramme, was developed to help oncologists in the selection of the systemic therapy regimen to which the patient's tumor would be most

Figure 3 Overview of the Frequency With Which Predictors Were Included in Decision Support System (DSS) for Incurable Metastatic Colorectal Cancer Patients



sensitive (Table 4). A proof of concept trial with a small sample of patients (n = 19) showed that this assay has good sensitivity (85%); however, the specificity was very low (33%). The congruence between the predicted and observed chemotherapy sensitivity was moderate (63%). The investigators reported plans for a large trial to obtain more insight regarding the usefulness of this tool.

User-friendliness of DSSs

Generally, the predictors incorporated in the DSSs identified were routinely collected in clinical practice (Table 4). Only the nomogram by Ichikawa et al[25] incorporated a genetic marker that is not yet routinely collected in clinical practice (ie, *UGT1A1* genotype). None of the DSSs were available as online tools. Although all DSSs can be derived from the development and/or validation reports, for 4 of the prognostic scores,[13,19,20,22] the scoring system and the breakdown into prognostic categories could not always be easily extracted from the reports.

Discussion

We performed a systematic review of the published data to obtain a comprehensive overview of the DSSs available to aid oncologists with palliative treatment decision-making for patients with incurable mCRC. We have provided insight into the characteristics of the available DSSs, their discriminatory accuracy and calibration, and their ease of use in clinical practice. Only 14 DSSs for patients with incurable mCRC were identified. The systematic search yielded many more DSSs aiming to guide treatment decision-making for

mCRC patients who might still be cured (eg, the Köhne score) using treatments such surgery with curative intent for solitary liver metastases or hyperthermic intraperitoneal chemotherapy plus cytoreductive surgery for peritoneal metastases. DSSs for treatments with a curative intent were not included in the present systematic review because our aim was to assess the state-of-the-art regarding DSSs for palliative treatment decision-making.

None of the DSSs for patients with incurable mCRC compared multiple treatment options. Of the 14 DSSs, 12 either aimed to help oncologists form an opinion on whether 1 specific treatment or further invasive palliative treatment in general is worthwhile, given the prognosis. One DSS assessed the risk of developing severe irinotecan-induced neutropenia, and one tool created individual chemotherapy sensitivity and resistance tumor profiles. We found no tool that encompassed multiple palliative treatment options available for incurable mCRC. Also, no repository containing all available DSSs for the palliative setting exists. Therefore, potentially informative resources might not find their way into clinical practice unless they have been incorporated into clinical treatment guidelines.

Furthermore, most of the tools focused on predicting survival. None presented both the benefits and harms of treatment. This is problematic, because DSSs are used by clinicians before patient consultations to better conceptualize the trade-off between the benefits and harms involved in treatment. DSSs can also be used during patient consultations to inform patients about their prognosis and help them to participate in the decision-making process. If DSSs only present the treatment benefits, it could cause both oncologists and patients to lose sight of the potential harms of the treatment modalities that target tumor progression. Maintaining and/or improving patients' quality of life is paramount and should be the cornerstone of palliative treatment decisions, in addition to patients' preferences. Additionally, other outcomes, such as quality-adjusted life expectancy, which are of interest from a societal and policy perspective were not included in any of the DSSs.

The predictors included in the DSSs varied greatly. Only age, performance status, and location of distant metastases were incorporated in ≥ 5 DSS. This in itself is not surprising because the DSSs have different aims. However, it is surprising that the predictors evaluated and those incorporated into the final model also varied among the DSSs that have the same aim (eg, the AAAP score, Dorajoo score, and Maeda score). This can be explained in part because almost all development studies had a retrospective design, which, thus, limited the availability of predictors. This could negatively affect a DSS' predictive ability. Furthermore, although 10 of 14 DSSs were developed within the past 5 years, only the nomogram by Ichikawa et al[25] included a genetic marker (ie, *UGT1A1* genotype). None of the DSSs included known clinically significant oncogenes (ie, *KRAS*, *BRAF*, or *PIK3CA*) or tumor suppressor genes (ie, *APC*, *TP53*, or *PTEN*).[31-35] Rapid developments in this field might make it difficult for DSS developers to remain current because the development and validation of DSSs are time-consuming processes. However, the addition of tumor markers could improve the discriminatory accuracy of DSSs.

Currently, evidence on DSS performance is limited owing to unclear reporting and methodologic problems. For example, some studies did not report basic characteristics regarding the patient population, such as the setting or year of diagnosis. Of the 14 tools, 9 only reached a Reilly level of evidence of 1, and 5 reached a level 2; thus, the DSSs were either not externally validated or only in a population very similar to the population in which the DSS was developed. Validation in > 1 ethnic population is also important because the medication metabolism and the probabilities of complications from surgery can differ owing to genetic and/or morphologic differences.[36,37] Three tools had been externally validated but were considered level 1, because the validation was poor (ie, the sample size was small [$n = 25$ and $n = 32$]) and/or the method was not sound. The method for determining the discriminatory accuracy of the DSSs varied among the studies, some investigators used Kaplan-Meier curves and log-rank tests, and others used receiver operating characteristic curves and C-indexes. Only 2 studies reported on the calibration, although this is an important measure of model performance. Moreover, the DSSs were developed for different purposes, and many were not externally validated. This makes it difficult to perform a meta-analysis or direct comparisons among DSSs.

The strength of the present review was the application of a broad search strategy to find all relevant tools. However, the lack of uniformity in terminology made it difficult to formulate a search strategy encompassing all relevant terms. This might have subverted our intent to retrieve all relevant DSSs. It is imperative that investigators work toward uniformity in terminology. Also, we had intended to use the CHARMS checklist[38] (checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies) to gain insights into the methodologic soundness of the DSSs. In preparation for the data extraction, we found that a large number of items included in the CHARMS checklist had not been reported or were not relevant to our purposes. Therefore, we opted to use a self-developed abbreviated version of the CHARMS checklist containing only the main points reported in Table 3.

Conclusion

The present review is, to the best of our knowledge, the first to provide a comprehensive overview of available DSSs aiming to aid oncologists' palliative treatment decision-making in the context of incurable mCRC. Our findings highlight the need for rigorously developed and validated comprehensive DSSs that compare multiple treatment options and provide insights regarding the benefits and harms of the treatment options. Ideally, newly developed DSSs would be continuously updated to keep up with the rapid developments in treatment. Embedding DSSs into national patient registries could facilitate their continuous update. Without exception, the use of existing DSSs in clinical practice cannot be recommended before establishing whether their discriminative ability is good and/or they have been validated in a broad range of populations (eg, different settings and ethnicities). Finally, impact studies are needed to gain insight into the effect of DSSs on clinical decision-making.

Clinical Practice Points

- Palliative treatment decision-making for mCRC is complex.
- DSSs, such as nomograms, can facilitate decision-making.
- Fourteen DSSs are available to aid decision-making regarding palliative treatment.
- None of available DSSs are currently appropriate for use in clinical practice.

- High-quality DSSs presenting both the benefits and the harms of treatment are needed.

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Disclosure

The authors have stated that they have no conflicts of interest.

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