SURGERY PROPOSALS IN ELDERLY COLORECTAL CANCER PATIENTS

A CLINICAL VIGNETTE STUDY

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PREFACE

The study “Surgery proposals in elderly colorectal cancer patients” was conducted from February to October 2016 in the Medical Spectrum Hospital Twente (MST) to finalize the Master in Health Sciences at the University of Twente (UT). The study methods and results are presented in this thesis, together with a discussion about the results and implications for clinical practice and (future) scientific research.

With guidance from my UT supervisors Maarten IJzerman and Janine van Til and my MST supervisor Machteld Wymenga, this study was designed and conducted with enthusiastic dedication. I would like to thank them for their help, feedback and motivation. They have enabled me to conduct this study in practice and they have motivated me to keep improving the quality of my work. I also would like to thank my family and friends for their moral support and many discussions, which were useful and valuable motivators. Of course, all respondents also deserve a word of thanks, because without them I wouldn’t have been able to conduct my study.

Now I hope you will enjoy reading this thesis.

Julia Keizer

Enschede, 5 October 2016

ABSTRACT

BACKGROUND Evidence-based treatment in older colorectal cancer (CRC) patients is difficult, because of under-representation of the elderly in clinical cancer trials. Next to this, multiple factors contribute to the heterogeneity of the elderly and therefore treatment proposals are complex. Considering geriatric assessments components (e.g. functional, cognitive and social functioning) together with other relevant criteria in elderly patients can assist physicians in making better treatment proposals in this patient group. Literature on whether and how additional geriatric information influences treatment proposals is scarce, while obtaining such information is time-consuming and expensive.

OBJECTIVES The aim of this study is to explore whether and how additional geriatric assessment information changes treatment proposals for older CRC patients by the multidisciplinary treatment team (MDT).

METHODS A rigorous mixed method approach was used to identify and select relevant proposal-criteria in older CRC patients. Results of a systematic literature review were combined with qualitative and quantitative clinical expert interviews. After careful analysis, six attributes that influence treatment proposals were selected for further analysis. The description of attribute-levels was based on clinical practice and existing measurements and these were validated using expert consultation. Attribute-levels were combined in clinical vignettes using a conjoint analysis rating approach. The clinical vignettes described patients, which were categorized as best, intermediate or worst candidates for surgery. Descriptive statistics, logistic regression analysis and the coefficient range method were used to analyze the results.

RESULTS In the systematic literature review 248 articles were reviewed full text. Most proposal-criteria were identified in the CGA category (n=422), followed by treatment (n=243) and disease (n=183) characteristics. The three most identified criteria were comorbidities (n=109), age (n=94) and functional status (n=84). 11 MDT members were interviewed. Experts often identified functional status (n=57) and comorbidities (n=41) as important proposal-criteria. This was also supported by the quantitative expert judgments of importance, in which comorbidities, social support and functional support were deemed important (82% scored very important). The attributes selected to describe patients eligible for surgery were age, cancer stage, comorbidities, functional status, cognitive status and social support. Based on the clinical vignettes, physicians (n=26) proposed surgery in the majority of clinical vignettes (71%). They changed their treatment proposals after considering the additional CGA information in 19% of the clinical vignettes. Patients were more likely not to receive surgery when they were older (85 years vs. 65 years; β:-3,368; p:0,006), had more comorbidity (severe comorbidity vs. no comorbidity; β:-3,459; p:0,003), had cognitive impairment (dementia vs. adequate cognitive status; β:-2,527; p:0,002) and had social support (no informal caregiver available vs. informal caregiver available; β:-2,956; p:0,011). In the coefficient range method the level of comorbidity (25%), age (24%) and social support (21%) had the highest part-worth utilities. Mean certainty for treatment propositions was lower after considering the additional CGA information and also in intermediate and worst candidates for surgery.

DISCUSSION Overall tendency to propose surgery was high and physicians agreed with each other in the majority of vignettes. Additional CGA information has little influence on the surgery proposal, because CGA information changed the surgery proposals in the minority of the chosen vignettes. Attributes that increased the likelihood of receiving surgery the most were comorbidity, age and social support. The relative importance of general information and CGA information was similar. Mean certainty decreased after considering the additional CGA information and also in intermediate and worst patient vignettes. Especially in these surgery candidates (identified with geriatric screening tools), CGA information should be considered. This enables making treatment proposals with more attention for elderly specific issues, which increases the quality of care for this older population.

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INTRODUCTION

BACKGROUND

Cancer is a common disease among the elderly (also referred to as the older population, traditionally defined as persons of 65 years and above (1)). In 2015, more than 45% of all new cancer patients in the Netherlands were aged between 60 and 75 years old, while 30% were aged over 75 years old (2). Because of the aging population and increasing life expectancy in almost all Western countries, the cancer incidence is likely to rise, especially among the elderly (3,4,5). This trend increases the burden on health systems, calling for effective and efficient resource allocation (6). One of the most common types of cancer is colorectal cancer (CRC) (7,8,9), with the 3rd highest incidence worldwide and 4th place in cancer-related mortality (apart from skin cancer) (10,11). Persons between 65 and 80 years comprise the peak incidence for CRC (12,13).

Medical guidelines state surgery as standard curative treatment for CRC, sometimes together with adjuvant chemotherapy (colon cancer) or pre- or postoperative radiation therapy and/or chemotherapy (rectal cancer) (9,14,15,16). However, the effect of these evidence-based approaches in older CRC patients is uncertain, because of the under-representation of (frail) older patients in clinical cancer trials (17,18,19). According to a 2015 systematic review more than half of all older cancer patients are (pre-) frail (5). Guidelines based on the trials available thus cover only a minority of the elderly population. In practice, this has resulted in elderly CRC patients being under-/over-staged and under-/over-treated (9,20). Different studies found a decrease in the deployment of (elective) surgical treatment and aggressive chemo/radiation treatments for cancer when age increased (21,22,23). This undertreatment is associated with decreased cancer-related survival rates in elderly rectal cancer patients (24).

Studies have shown however that chronological age per se is not a negative prognostic factor for CRC treatment, because fit elderly derived the same benefit from treatment as younger CRC patients (25,26,27,28). The elderly population is heterogeneous with regard to (geriatric) comorbidity, physical reserves, disability and poly-pharmacy (9,29). Moreover, patients and their families have various preferences for their remaining life time (30,31,32). These individual differences in treatment tolerance, effectiveness and preferences therefore call for individualized treatment proposals (17,33,34). Although seemingly counterintuitive in

some cases, effective management of cancer can include not receiving treatments that are considered effective in the general population, such as surgical intervention (35). This might reduce premature mortality, prevent functional decline and decrease the need for hospitalization and futile and sometimes costly interventions in the elderly (9,17,36,37).

Physicians thus are challenged to determine the optimum treatment strategy for elderly patients (9,29). By distinguishing fit from more frail patients, CRC treatments can be adjusted to meet the individual requirements of the patient (5,38,39). The International Society of Geriatric Oncology (SIOG) therefore recommended preoperative evaluation for all CRC patients >65 years, focused on the most common physiological side-effects of aging, physical and mental ability and social support (9). Additionally, a geriatrician should further assess patients indicated with psychological or physical comorbidities.

The Dutch Health Care Inspectorate (IGZ) also emphasized this in their “Basic set quality indicators hospitals 2016”. Several indicators focus on the frail elderly in general and two specifically focus on frail elderly CRC patients undergoing surgery (40). All CRC patients ≥70 years should be screened on four components of frailty (risk of delirium, falling, malnutrition and functional loss) using short geriatric assessment tools (ISAR-HP or G8) and if a patient seems to be frail, a comprehensive geriatric assessment (CGA) should be performed by a physician with a focus on older patients (e.g. geriatrician).

A CGA is *“a multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described, and explained, if possible, and in which the resources and strengths of the person are catalogued, need for services assessed, and a coordinated care plan is developed to focus interventions on the person's problems”* (33,41).

RESEARCH PROBLEM

It is up to the multidisciplinary treatment team’s (MDT) discretion to use and weigh the results of the CGA in defining an optimal treatment plan (41). This isn’t easy, since other factors also influence the treatment proposals, such as medical considerations (e.g. type and stage of tumor) (30,35,42,43), patient and relative preferences (30,31,32), economic considerations (both on society level and on patient level) (30,44,45,46) and physician-related factors (e.g. personal beliefs and experience) (30). These factors cause the treatment proposals to become complex and multi-facetted. Studies have found that MDT

cancer treatment proposals are medically dominated and focus primarily on the cancer pathology (47,48). This reflects the intuitive approach that MDT members use to simplify complexity (47,49). In such approaches however, important information, like information from geriatric assessments, could be ignored (49). Inconsistency, variability and a lack of predictability of the influence of proposal-criteria may exist without a formal evaluation process and this might lead to suboptimal treatment proposals (50). This was supported in exploratory interviews with a medical oncologist, a surgeon and a geriatrician. They explained that they don't know how additional CGA information influences their treatment proposals, while obtaining such information is time-consuming and expensive (51).

Literature on the influence of geriatric assessments on the final treatment proposal for older CRC patients is scarce. In a systematic review, Puts, et al. (52) found only four studies examining the influence of CGA before the start of the treatment on the final cancer treatment plan. In two studies CGA influenced the final treatment plan, mostly by altering the chemotherapy regimen (53,54). In the other two studies, CGA didn't change the treatment plan (55,56). An updated search identified 5 other studies, in which treatment plans were all adapted after CGA (see appendix 6). To our best knowledge, other studies on the influence of geriatric assessments on treatment proposals in elderly CRC patients haven't been performed so far.

OBJECTIVES

Because of this fuzziness and paucity of evidence, it is important to increase understanding of treatment proposals for elderly patients and how geriatric assessments influence such proposals. Therefore, the goal of this study was to show whether and how CGA results influence MDT members' treatment proposals for older CRC patients. The following research question was central to this study:

How does additional information of geriatric assessments influence treatment proposals of members of the multidisciplinary treatment team for older (≥65 years) colon cancer patients?

A second goal of this study was to apply a rigorous approach to identify and select relevant proposal-criteria in older CRC patients.

METHODS

In the first phase of this study, factors (named criteria hereafter) that influence the proposal for surgery in elderly CRC patients were elicited with a systematic literature review and expert interviews. In the second phase of the study, clinical vignettes were designed using stated preference (SP) methods to identify and evaluate the relative importance of the criteria (or attributes) that influence the surgery proposal in a descriptive proposal analysis. Steps for developing, analyzing and publishing SP studies from the ISPOR Conjoint Analysis Task Force Report were followed in this study (see figure 1) (57).

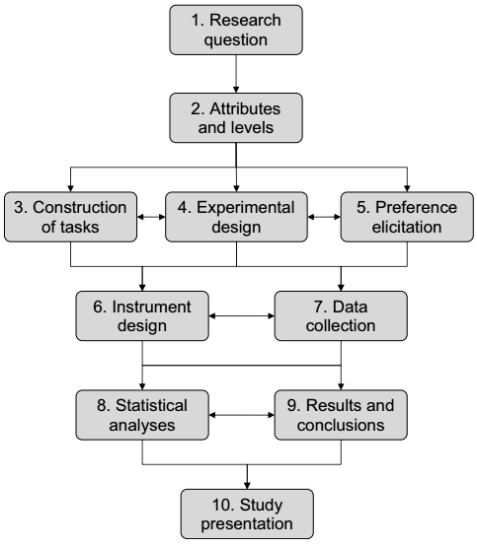


Figure 1. ISPOR checklist for conjoint analysis in health care (57).

IDENTIFYING PROPOSAL-CRITERIA

SYSTEMATIC LITERATURE REVIEW

A systematic review of articles in PubMed, Scopus and Web of Science was performed. Checking reference lists of the retrieved studies identified additional studies. Key search terms included (synonyms and combinations of): colorectal cancer, elderly, treatment and decision. “Screening” was excluded as search term, because many articles were related to the discussion about screening for CRC, which was considered irrelevant to the current research question. All articles identified were assessed based on the title and abstract.

Articles that focused on diagnosing, specific treatments, other (non-cancer) diseases, information and informed consent, after-care, trials and research were excluded, because proposal-criteria identified in these articles weren’t applicable to the proposed research question. Other articles were excluded, because they weren’t freely available full text, because no abstract was available or because they weren’t in English, Dutch or German. All other articles were fully read by one researcher.

Articles weren’t assessed on the type of study or quality criteria, because of the explorative and descriptive character of this review; the goal was to get a broad range of possible proposal-criteria, which were further assessed in interviews to assure the feasibility and

relevance. Identified proposal-criteria were categorized (e.g. medical, patient-related, etc.) and quantified.

CLINICAL EXPERT INTERVIEWS

The results of the systematic literature review served as input for individual interviews with all stakeholders relevant to the treatment proposal for CRC patients (i.e. the MDT: medical oncologist, geriatrician, surgeon, gastroenterologist, radiologist, radiation oncologist, case manager CRC and oncology nurse (14)). In these semi-structured interviews, the current proposal-process and the results of the systematic literature review were qualitatively discussed (see appendix 1). Experts were asked about additional important criteria that were missing from the systematic literature review.

All interviews were recorded, transcribed and coded in ATLAS.ti (version 7.5.12). The coded criteria were categorized and quantified in the same manner as the systematic literature review, which allowed easy and objective comparison of both results (see appendix 2).

At the end of each interview, the results of the systematic literature review were presented and respondents were asked to score the importance of all criteria in the treatment proposal for older CRC patients on 5-point Likert Scales (1: Not important - 5: Very important). This was done, because it turned out to be difficult for the clinical experts to denominate proposal-criteria. They explained that most of these proposal-criteria are implicitly considered (often referred to as the “clinical eye”) (58,59). Overviews of the percentage per answer possibility were calculated and presented in a bar chart to visualize the importance of the different proposal-criteria and the dissension about each proposal-criterion.

SELECTION OF ATTRIBUTES

In order to select attributes for the clinical vignettes from the identified proposal-criteria, the following quality aspects were assessed: relevance to research question, relevance to proposal context (content validity), completeness, mutual independency, operationality, size and redundancy. The aim was to select five to seven attributes, because this reflects the average number of attributes included in similar studies and this number is believed to be acceptable for respondents to handle (60).

The quantified proposal-criteria of the systematic literature review and interviews were ranked from highest frequency to lowest and compared with the proposal-criteria with the highest percentage of combined scores 4 and 5 on the Likert Scale (scores “Important” and “Very important”). Proposal-criteria were selected as attributes based on the top 10 of these rankings. These results were discussed with two researchers and a medical oncologist until consensus was reached about the selection of attributes.

DESIGN OF THE CLINICAL VIGNETTE STUDY

A commonly used method to study treatment proposals is the use of structured clinical vignettes. Such vignettes are believed to reflect treatment proposals in clinical practice and its results strongly predict actual behavior. Other advantages of this method are its ease of use, low costs and its ability to overcome ethical, practical and scientific limitations that other methods experience (e.g. time-consuming case record analysis, non-revealing observations or socially desirable self-reports) (61,62,63,64).

SELECTION OF ATTRIBUTE-LEVELS

The description of attribute-levels was based on how information about the attributes is obtained by clinical experts in practice, so that realistic, reliable clinical vignettes could be made on clinical practice and existing measurements and these were validated using expert consultation. In deciding how many clinical vignettes needed to be answered by respondents, statistical efficiency was balanced against response efficiency (57,65,66). Therefore, the maximum number of levels per attribute was set to three, which allowed for reasonable differentiation between attribute-levels, but were manageable for the respondents.

CONSTRUCTION OF TASKS & PREFERENCE ELICITATION

Selected attributes were: age, comorbidity, cancer stage, functional status, cognitive status and social support.

Stated preference studies can use conjoint analysis (CA) tasks, such as rating, ranking or choice-based tasks (57). In practice, experts don’t base their treatment proposal on the comparison of each attribute (-level) as in ranking studies or the comparison between two patients as in choice-based studies. Furthermore, CGA information is not available for all patients at all times since only some older patients are referred to a geriatrician for CGA and in practice CGA often occurred after the MDT treatment proposal.

Therefore, clinical vignettes were divided into two parts, each followed by two rating choice tasks (questions A/B/C/D):

1. In part 1 general information that physicians always demand to determine a treatment plan (age, comorbidities and cancer stage) was shown, followed by questions A&B:
    A. Respondents were asked if they would propose surgery, based on the general information.
    B. Respondents needed to rate the certainty about their proposal on a scale from 1 (Not sure) to 5 (Very sure).
2. In part 2 additional CGA information (functional status, cognitive status, and social support) was shown; followed by question C and D:
    C. =Question A after additional CGA information
    D. =Question B after additional CGA information

Questions A and C were used to elicit preferences and qualifying questions B and D were used to assess the level of confidence in the answers of the previous questions (57). By doing this, the surgery proposal itself and the certainty about this proposal without and with CGA information could be compared. An example of one full vignette (part 1 + part 2) with questions is shown in figure 2.

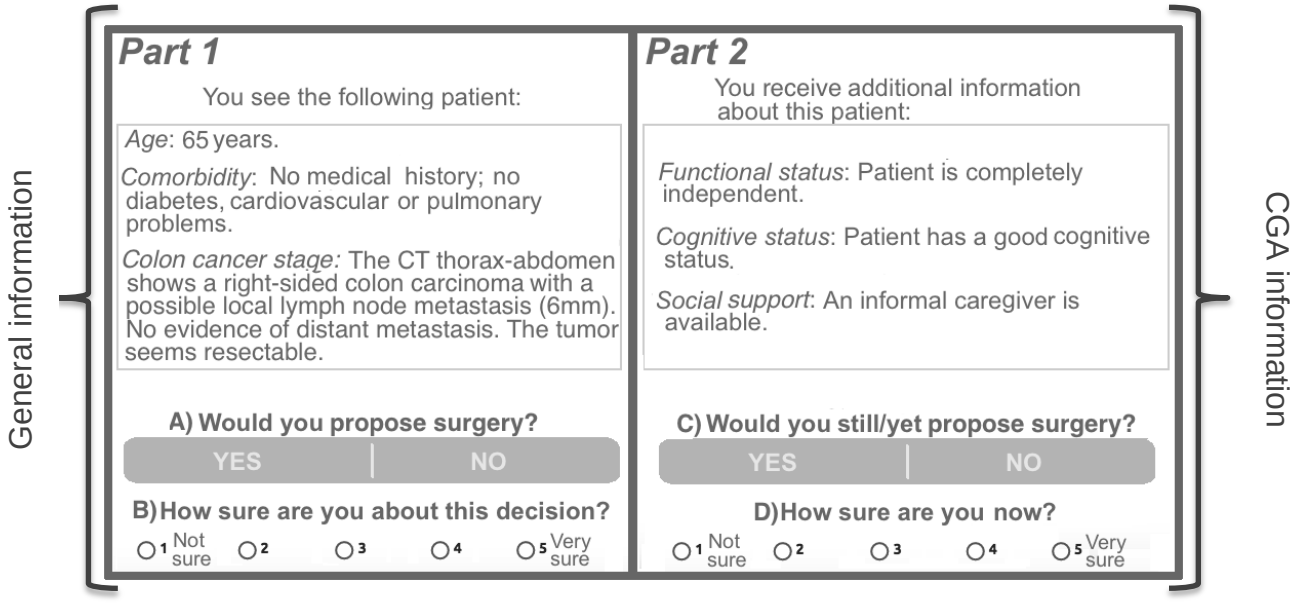


Figure 2. Example vignette

Full vignettes (all attributes per vignette) were shown. No-opt out possibility was given, because in real-life MDT members also don't have an opt-out option.

EXPERIMENTAL DESIGN

Good CA designs are both orthogonal (all attribute levels vary independently) and balanced (each attribute-level occurs the same number of times) (57). In total there were 16 attribute-levels and these could be combined into (3^4*2^2) 324 vignettes. A full factorial design of 324 vignettes was not feasible. The respondent sample was expected to be between 20 and 50 respondents, which is considered low for a CA study (67). Therefore, it was decided to test for main and most important effects only in this pilot study. A fractional factorial design was hand-made and a block design (splitting up part 2 in 2 versions) was used to enable the inclusion of more combinations (see table 1).

TABLE 1. EXPERIMENTAL DESIGN

Section	Vignette	Part 1 (Version 1 = version 2)			Questions	Part 2						Questions
						Version 1			Version 2			
		Age[1]	Cmb[2]	Stage[3]		FS[4]	CS[5]	SS[6]	FS[4]	CS[5]	SS[6]	
1	1	1	1	1	1: Would you propose surgery? 2: How sure are you about this proposal?	3	3	2	= Version 1			3: Would you still/now propose surgery? 4: How sure are you now?
	2	3	3	2		1	1	1	= Version 1			
2	3	2	2	1		3	2	2	2	3	1	
	4	1	3	1		2	1	1	1	2	1	
	5	3	1	2		2	3	1	1	1	2	
	6	2	2	2		1	2	2	3	1	2	
	7	1	3	2		1	1	2	2	3	2	
	8	3	1	1		3	3	1	3	2	1	
3	9 (=1)	1	1	1		3	3	2	= Version 1			
	10 (=3)	2	2	1		3	2	2	2	3	1	

[1]Age (1=65 years; 2=75 years; 3=85 years), [2]Comorbidity (1=None, 2=Mild, 3=Severe), [3]Stage (1=Mild, 2=Severe)
[4]Functional status (1=Independent, 2=Some help, 3=Dependent), [5]Cognitive status (1=Adequate, 2=Forgetful, 3=Dementia), [6]Social support (1=Informal caregiver available, 2=Informal caregiver not available)

Best candidate for surgery (sum attribute-levels ≤4)	Intermediate candidate for surgery (other)	Worst candidate for surgery (sum attribute-levels ≥7)

The clinical vignette design could be split up in three sections and proposals about the content of each of these sections were based on the following assumptions:

1. The first section consisted of dominant vignettes 1 and 2, which allowed assessing the response quality and internal validity:
    a. In the first clinical vignette the hypothetical best surgery candidate (lowest age, no comorbidity and mild cancer stage) was combined with the worst geriatric assessment (dependent functional status, dementia and no social support). It was

assumed that if a respondent did not propose surgery based on the best surgery candidate in part 1, they would not propose surgery for any of the vignettes.

b. In the second clinical vignette the hypothetical worst surgery candidate (highest age, severe comorbidity and severe cancer stage) was combined with the best geriatric assessment (independent functional status, adequate cognitive status and social support). It was assumed that if a respondent did propose surgery based on the worst surgery candidate in part 1, they would propose surgery for any of the vignettes.

2. The second section consisted of six vignettes with mixed attribute-levels without extremes. Part 1 and 2 were each balanced, but not orthogonal. An illogical combination (in which a patient had dementia (CS level 3), but was fully independent (FS level 1)) was blocked in the design, making it impossible to assure orthogonality in only 6 vignettes (57,60,66). Balance thus was given priority over orthogonality.
3. The third section consisted of two duplicate vignettes to measure intra-rater reliability. Vignette 9 was a duplicate of vignette 1 and vignette 10 of vignette 3.

These sections resulted in 10 vignettes to be reviewed by respondents, corresponding with CA good practice in healthcare (57). The number of vignettes was limited, because respondents were also asked to fill in demographic information and because explaining the conjoint tasks cost considerable time. In two face-to-face pilot-tests with a medical oncologist and a surgeon, this showed to be an appropriate number of tasks.

To make comparisons between vignettes clearer, vignettes parts were classified as “best candidate for surgery” (summed attribute-levels ≤4), “intermediate candidate for surgery” (other) or “worst candidate for surgery” (summed attribute-levels ≥7). This is reflected in the colors of the cells in tables 1 and 6 and figures 6 and 7. Furthermore, vignettes as a whole (general + CGA information) were classified as best candidate for surgery” (summed attribute-levels <10), “intermediate candidate for surgery” (other) or “worst candidate for surgery” (summed attribute-levels >12).

INSTRUMENT DESIGN

The questionnaire was built and administered in LimeSurvey (version 2.50+). Socio-demographic characteristics (gender, age, profession, work experience in years and

number of new CRC patients seen per month) were collected to test for systematic differences in answers based on these characteristics (57).

In the introduction of the questionnaire, the overall of the study and the attributes and levels were presented. In the explorative interviews, many experts explained that they needed to see a patient in person to assess his/her health to determine a treatment plan. Therefore, it was explicitly stated in the introduction that it was understood that the respondents needed to examine the patient to determine an optimal treatment plan, but they were asked to fill out the questionnaire as realistic as possible based on the data available in the vignettes.

Detailed face-to-face pre-tests were held with a medical oncologist and a surgeon to identify practical and interpretative problems and to test the perceived appropriateness of the test. This resulted in adaptions of the introduction text (less information) and layout of the answer options (more intuitive design). It took around 15 minutes to complete the questionnaire.

DATA COLLECTION

Because CA sample size calculations in healthcare are still being studied and no consensus has been reached, rules of thumb are still employed (57,66). The desired sample size depends for example on question formats, complexity of the choice tasks, available respondents and desired precision of results (57,66,68). Because of thesis related time constraints, the clinical vignette study is a pilot-study with a limited sample size and simplified calculations. Therefore, the traditional guideline for events per predictor variable (EPV) was used, which prescribes that logistic regression analysis should include at least 10 events per predictor variable (EPV) (69,70). This meant that at least 160 (=16 attribute-levels*10 EPV) observations were needed. Because each questionnaire consisted of 8 unique observations (=10-2 duplicates), 20 (=160/8) respondents were needed.

In the explorative interviews it became clear that MDT radiation oncologist and pathologists don’t actually contribute to final treatment proposals and that their clinical knowledge didn’t cover such proposals. They have a supportive role, because they present the radiologic/pathologic data in the MDT, but don’t give advices based on their findings. Therefore, they were excluded from the study group. An email with a link to the LimeSurvey questionnaire was sent to all other CRC MDT members in the MST hospital (n=55). The

questionnaire versions were randomly assigned to respondents per function category. The first mailing was sent on the 21st of July, after which two reminders were sent (8th of August and 29th of August).

STATISTICAL ANALYSIS

This study's primary goal was to analyze the influence of the geriatric assessment (i.e. functional status, cognitive status and social support) compared to other proposal-criteria (i.e. age, comorbidity and cancer stage) in surgery proposals. This was analyzed with a logistic regression model. Because of the small sample size, descriptive statistics were also used to analyze the questionnaire responses. All calculations are shown in appendix 4 and described below. SPSS (version 23) was used for all calculations.

RESPONDENT CHARACTERISTICS

Respondent characteristics were assessed using descriptive statistics: mean age, work experience and the number of new CRC patients per month seen, together with their standard deviations (SD) and maximum and minimum values. Ratios were calculated for respondents' gender and function. To test for systematic differences in answers based on these characteristics, split-sample analysis was performed, based on the respondents' function and experience (57).

QUALITY OF RESPONSES

To assess the quality of responses (internal validity), three aspects of the questionnaire were evaluated. First, the answers to the dominant best vignette 1 (general information) were analyzed to test respondents' comprehension with the method. If respondents didn't answer "yes" to the first question, their results were excluded from analysis. Second, the intra-rater consistency was checked by analyzing the consistency between answers for the duplicate vignettes (1-9 and 3-10) per respondent with a Wilcoxon Signed Ranks Test. Third, inter-rater consistency was assessed using intra-class correlation (ICC; two-way random effects model).

SURGERY PROPOSALS PER VIGNETTE

Descriptive statistics were used to analyze the proposals per vignette. First, the percentage of patients that would have received surgery was calculated overall to see the general tendency of the surgery proposals. Second, a rank biserial correlation was used to assess the relationship between surgery choice and certainty about this choice. Third, changes in

proposals between part 1 (general information) and part 2 (CGA information) were analyzed to see the influence of the additional CGA information on the surgery proposal. Last, agreement between physicians about their surgery proposal per vignette was analyzed. Agreement was defined if surgery was (not) proposed by ≥80% of the respondents and disagreement was defined as surgery proposed by 40%-60%.

EFFECT OF VIGNETTES ON LIKELIHOOD OF RECEIVING SUGERY AND RELATIVE IMPORTANCE

Binomial logistic regression was performed to ascertain the effects of all attribute-levels on the likelihood that patients would receive surgery (question 3). Because there were no continuous independent variables, no check was needed to assure that the independent variables were linearly related to the logit of the dependent variable. Outliers were tested by using case diagnostics (studentized residuals). The model was also tested on statistical significance (Omnibus Tests of Model Coefficients) and variance explanation (Nagelkerke R^2).

Independent variables (attribute-levels) were all coded as categorical data, because they all represented ordered levels (with the first level being "good" and the last level being "bad"). Dummy variables were used for the independent variables, because this method is more familiar in health care research than effects coding (57). Significance levels were set at p=0,05.

The relative importance of each attribute was calculated with the coefficient range method. In this method, the coefficient range per attribute is calculated and summed up (total range). Then the proportion of the coefficient range of each attribute compared to the total range is calculated and the attribute with the highest proportion is the most important.

REQUESTED ADDITIONAL INFORMATION

In the last question of the survey respondents could select additional information that they wanted to collect about the patient to improve their proposals. The answers could shed light on which criteria are deemed important next to the criteria included in the questionnaire.

RESULTS

PROPOSAL-CRITERIA AND ATTRIBUTES

SYSTEMATIC LITERATURE REVIEW

The search of PubMed, Scopus and Web of Science provided 1021 unique citations. Based on the exclusion criteria, 773 were excluded, leaving 248 citations to be reviewed full text. During reviewing these citations full text, 74 were excluded based on the mentioned exclusion criteria. In the end results of 174 citations were included in the systematic literature review. This is shown in figure 3.

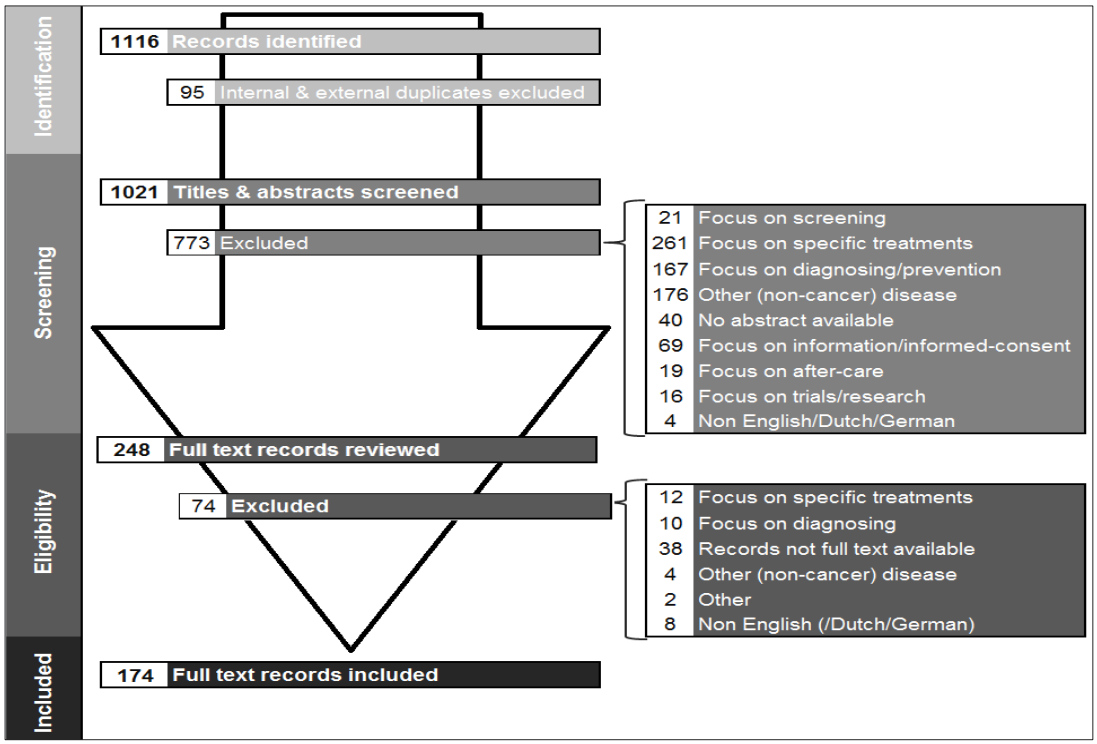


Figure 3. Overview systematic literature review

Identified proposal-criteria could be divided into 8 categories: patient characteristics, preferences, costs, CGA components, treatment characteristics, disease characteristics, social support and physician factors. Most proposal-criteria were found in the CGA components category (n=422), followed by the categories treatment (n=243) and disease characteristics (n=183). All identified proposal-criteria can be found in figure 4.

Because treatment characteristics (e.g. expected outcomes) are implicitly anticipated in the treatment proposal based on the other proposal-criteria, but can't be explicitly chosen in the treatment proposal, these were further excluded from quantification in the results of the

literature study, interviews and Likert Scales. This also applies to the physician characteristics, since these are criteria, which might influence the treatment proposal (e.g. physician experience), but can't be explicitly chosen in the treatment proposal.

CLINICAL EXPERT INTERVIEWS

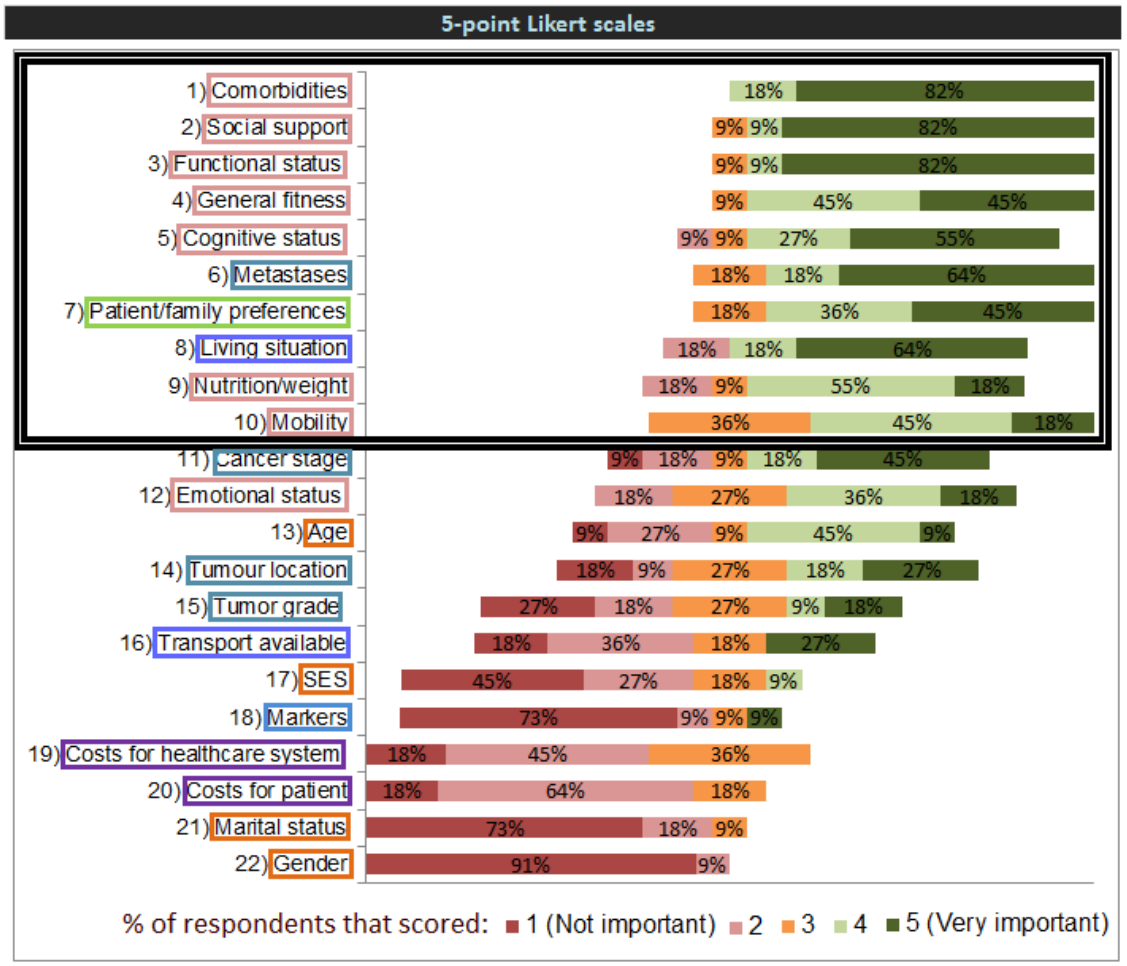
Interviews were held with 11 clinical experts of the multidisciplinary cancer team (2 surgeons, 2 medical oncologists, 2 gastroenterologists, 2 radiation oncologists, 1 radiologist, 1 case manager CRC and 1 oncology nurse) from the top-clinical hospital Medical Spectrum Twente (MST) in Enschede, the Netherlands.

Identified proposal-criteria were categorized according to the same categories as in the systematic literature review. Most proposal-criteria were found in the CGA components category (n=183), followed by the categories treatment (n=95) and disease characteristics (n=36).

Additional criteria brought up by the clinical experts, that weren't acknowledged in the literature study were: specific screenings tests (e.g. pre-sedation checklist, thyroid test, electrocardiography), patient understanding and confidence in treatment-handling (does the patient at least understand the diagnosis and treatment plan and will he/she contact the care professional in case of problems) and stress (-coping). Furthermore, all physicians mentioned their "clinical eye" as an important, if not most important, factor in their evaluation of a patient. This is for example illustrated by the following quotes: "I prefer having my examination room as far as possible from the waiting area, because I can determine the patient's state and treatment resilience while he/she walks from the one to the other" and "Ideally, I would like to ask all my patients to get undressed and dressed, even though this isn't necessary for examinations. By doing this, I can see how their physical condition actually is".

All clinical experts filled in the Likert Scales. The quantified results of the systematic literature review, interviews and Likert Scales are presented in figure 4. The top 10 of each method is delineated with a thick black line (with a shared tenth place in the literature study).

Literature study		Rank	Interviews	
Criteria	#		Criteria	#
Comorbidities	109	1	Functional status	57
Age	94	2	Comorbidities	41
Functional status	84	3	Lifestyle	23
Stage	52	4	Age	19
Physiologic	49	5	Patient preferences	15
Lifestyle	45	6	Cognitive status	14
Patient preferences	38	7	Location	14
Cognitive status	35	8	CGA	13
CGA	29	9	Prognosis	10
Location	27	10	Physiologic	9
Cluster social support	27		Cluster social support	8
Imaging/histopathology findings	26	12	Metastasis	8
Metastasis	22	13	Psychological	8
Markers	18	14	Living situation	7
Psychological	16	15	SES	6
ASA	15	16	Imaging/histopathology findings	5
Emotional status	14	17	Dependency	5
Prognosis	14	18	Costs	4
Grade/differentiation	13	19	Symptoms	4
Gender	13	20	Family members'reports	4
SES	11	21	Stage	2
Costs	10	22	Family preferences	2
Symptoms	9	23	Fatigue	2
Family preferences	9	24	Size	2
Transportation	9	25	Markers	1
Bowel status	8	26	ASA	1
Marital status	8	27	Gender	1
Dependency	7	28	Falling	1
Living situation	7	29	Emotional status	0
Fatigue	6	30	Grade/differentiation	0
Falling	6	31	Transportation	0
Race	6	32	Bowel status	0
Presentation	4	33	Marital status	0
Size	4	34	Race	0
Family members'reports	0	35	Presentation	0



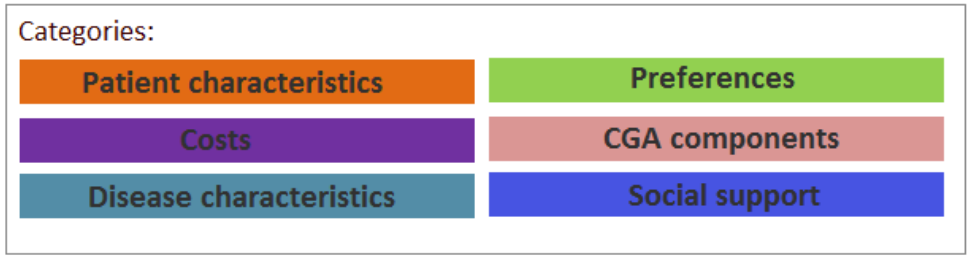


Figure 4. Results and top 10-comparisons of the systematic literature review, interviews and Likert scales.

SELECTION OF ATTRIBUTES

As can be seen in figure 4, the top 10 of the three parts are quite similar. Proposal-criteria that were in the top 10 of all three results were: comorbidities, functional status, lifestyle/nutrition/weight, cognitive status, patient preferences and CGA/frailty/fitness in general. Proposal-criteria that were in at least two out of three top 10's were: age, social support, physiologic status and tumor location.

All the high-ranked proposal-criteria and their interdependencies (dotted lines) are shown in figure 5. Some proposal-criteria are directly linked to each other: if a patient has a lot of comorbidities, it is likely that he takes several medications (polypharmacy), if a patient has a poor functional status or cognitive decline, it is unlikely that he lives independently (living situation) and if a patient is married, it is likely that there is social support (informal caregiver available). These interdependencies are important in selecting proposal-criteria, because attributes should be *mutual independent* and illogical or impossible combinations should be avoided (*operationality*) (57,60,66).

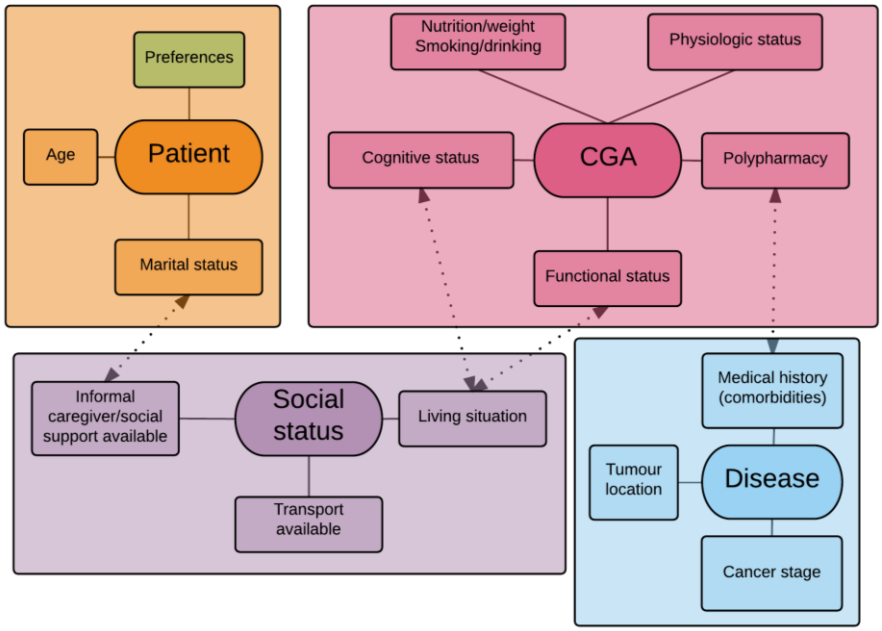


Figure 5. Proposal-criteria overview

Other criteria were adapted (tumor location) or excluded (patient preferences) because of their irrelevance to the research question. It became clear in the interviews that tumor location was considered important, because it distinguished colon from rectal cancer. Within in the colon or rectum however, the location was of less, even negligible importance. Because treatment strategies for colon cancer and rectal cancer are different and because colon cancer has more straightforward, standard and technically less demanding treatment plans than rectal cancer (39,71), the clinical vignette study focused on colon cancer (CC). Patient and family preferences were excluded, although they are essential and mostly even prevail in the treatment process (which was also reflected in the results of all three study

methods). If a patient refuses treatment, then the MDT can advise on optimal therapy only. The other way around, if a patient insists on receiving a treatment, but his/her characteristics don't allow it, because of safety reasons for example, the MDT can never decide to treat, because they are bound to their professional Hippocratic Oath and laws for good medical practice (72).

In consensus with two researchers and a medical oncologist, the following six attributes were selected: age, cancer stage, comorbidities, functional status, cognitive status and social support. For each attribute different levels were designed. All attributes and attribute-levels are shown in table 2 and are further elaborated on in appendix 4.

TABLE 2. ATTRIBUTES AND ATTRIBUTE-LEVELS PART 1 AND 2

	Attributes	*Levels*
Part 1: General information	Age	65 years
		75 years
		85 years
	Comorbidity	Blanc medical history; no diabetes, cardiovascular or pulmonary problems.
		Patient has COPD Gold II and diabetes mellitus since 2 years (oral medication), but has no cardiovascular complications.
		Patient has COPD Gold III and insulin-dependent diabetes mellitus since 15 years. Patient has a conservative policy for peripheral vascular disease. Patient had a myocardial infarct 4 years ago with atrial fibrillation and a moderate liver function afterwards (35-40%). Patient had a TIA two years ago.
	Cancer stage	The CT thorax-abdomen shows a colon carcinoma on the right side with a possible local lymph node metastasis (6mm). No evidence of distant metastases. The tumor seems resectable.
		The CT thorax-abdomen shows a colon carcinoma on the right side with several enlarged lymph nodes. There are liver metastases (3 left and 1 right), but these seem resectable. Patient has stomach-aches regularly and is often nauseous. The defecation pattern has clearly changed. There is an iron deficiency anemia for which transfusion was given recently. The local problem has priority.
Part 2: CGA information	Functional status	Patient is completely independent.
		Patient needs help with putting on stockings and has domestic help once a week.
		Patient has domiciliary care twice a day for (un-) dressing and washing, domestic help once a week and obtains meals from “meals on wheels”.
	Cognitive status	Patient has a good cognitive status. (MMSE 30/30).
		Patient is a bit forgetful, but can cope with it well (MMSE 26/30).
		Patient has dementia (MMSE 18/30).
	Social support	An informal caregiver is available.
		No informal caregiver is available.

RESULTS CLINICAL VIGNETTES

RESPONDENT CHARACTERISTICS

Respondent characteristics are shown in table 3. In total 26 respondents filled in the questionnaire completely (response rate 47%) resulting in 260 observations. More women than men filled in the questionnaire and respondents were 46 years old on average. Of all MDT professions, at least one of each was included. Respondents had an average of 12

years work experience in their current profession and monthly they see 6 new CRC patients on average. Respondent characteristics were similar between version 1 and 2 of the questionnaire.

TABLE 3. DEMOGRAPHIC CHARACTERISTICS OF RESPONDENTS

Characteristics		*Total*	*Version 1*	*Version 2*
	Total, N (%)	26 (100)	15 (58)	11 (42)
Gender, N (%)	Women	16 (61)	9 (60)	7 (64)
	Men	10 (38)	6 (40)	4 (36)
	Mean (SD) age (years)	45,9 (8,5)	45,1 (8,2)	46,9 (8,7)
Function, N (%)	Case manager	1 (4)	0 (0)	1 (9,1)
	Surgeon	5 (19)	2 (13)	3 (27,3)
	Geriatrician	2 (8)	1 (7)	1 (9,1)
	Medical oncologist	7 (27)	4 (27)	3 (27,3)
	Gastroenterologist	4 (15)	3 (20)	1 (9,1)
	Radiation oncologist	5 (19)	4 (27)	1 (9,1)
	(Oncology) nurse	2 (8)	1 (7)	1 (9,1)
Experience, mean (SD)	Work experience (years)	12,1 (10,7)	12,5 (10,9)	14 (14,5)
	Newly diagnosed CRC patients seen per month	5,8 (5,8)	6,6 (5,8)	4.73 (5,5)

QUALITY OF RESPONSES

Based on the exclusion criterion for the best surgery candidate (part 1), no respondents were excluded, because 100% of the respondents proposed surgery and certainty was high (mean: 4,9 & SD: 0,3). The assumption for the best patient vignette (part 1) thus was met. Unexpectedly, the assumption for the worst patient vignette (part 1) was not met. Six respondents proposed surgery for the worst patient, while they did not propose surgery for a patient with a better vignette. This better vignette was the same for all respondents and it represented an intermediate vignette (vignette 7). These vignettes 2 and 7 have the same comorbidity-level and cancer stage (both worst levels), while age differs (between the worst level in vignette 2 and best level in vignette 7).

TABLE 4. INTRA-RATER CONSISTENCY (DUPLICATE VIGNETTES)

Parts	Question	Duplicate vignettes	
		1&9	10 vs. 3
1: General info	A[a]	100%	100%
2: CGA info	C[a]	81%	92%

a) % of respondents that answered the duplicate vignettes the same

Differences between duplicate vignette answers were found, but none were statistical significant (appendix 6). The percentage of respondents that answered the duplicate vignettes the same was quite high (see table 4), especially when respondents considered the general info only (100%). Intra-rater consistency thus was high.

The ICC score was 0,91 (95% CI: 0,81-0,97) for question A and 0,86 (95% CI: 0,69-0,96) for question C. Because an ICC score of 1 reflects excellent agreement, inter-rater consistency in this study was high.

Because of respondents' good comprehension of the vignettes and high intra- and inter-rater consistency, response quality was considered high.

SURGERY PROPOSTITIONS PER CLINICAL VIGNETTE

In figures 6 and 7, overviews of the vignette designs, corresponding surgery proposals and certainty about these surgery proposals are shown per vignette (1-10). Figure 6 focuses on the overall surgery proposal, based on the general and CGA information together (question C-D). Figure 7 focuses on these parts separately (question A-B and C-D). Because different vignettes were shown in version 1 and version 2 of the questionnaire, the results are shown separately per version.

Overall surgery proposal was high, since almost all patients would have received surgery according to the respondents based on the general and CGA information (see figure 6; overall 71% "Yes" to question C). Moreover, surgery was proposed by half (53%) of the physicians based on the general information of the worst surgery candidate, despite its bad attribute-levels (figure 7).

Surgery proposals are weakly, but statistical significant correlated to certainty scores (see table 5). This means that positive treatment proposals are made with (slightly) more certainty than negative treatment proposals. This can be seen in figures 6 and 7 as well, since all 100% positive surgery proposals are followed by high certainty scores.

TABLE 5. CORRELATION BETWEEN CHOICE AND CERTAINTY

	General info (part 1)	CGA info (part 2)
Correlation value	0,265	0,249
Sig. (2-tailed)	<0,01	<0,01

Additional CGA information changed the surgery proposal in only 19% of the vignettes, mostly from "yes" to "no" (18%). Physicians were more certain about their proposal based on the general information compared to when additional CGA information was shown (mean certainty part 1: 4,08 & mean certainty part 2: 3,56). This is also reflected in figure 7, since certainty scores are centered more to the right and less wide.

In half of the vignettes, physicians agreed (≥80% same answer; see figure 6) about the patient (not) receiving surgery. Physicians disagreed (40%-60% proposed surgery; see figure 6) on 4 vignettes, which represented intermediate to worst surgery patients. This is also reflected in figure 7, since proposals around the 50% mostly occur in intermediate to worst vignette parts.

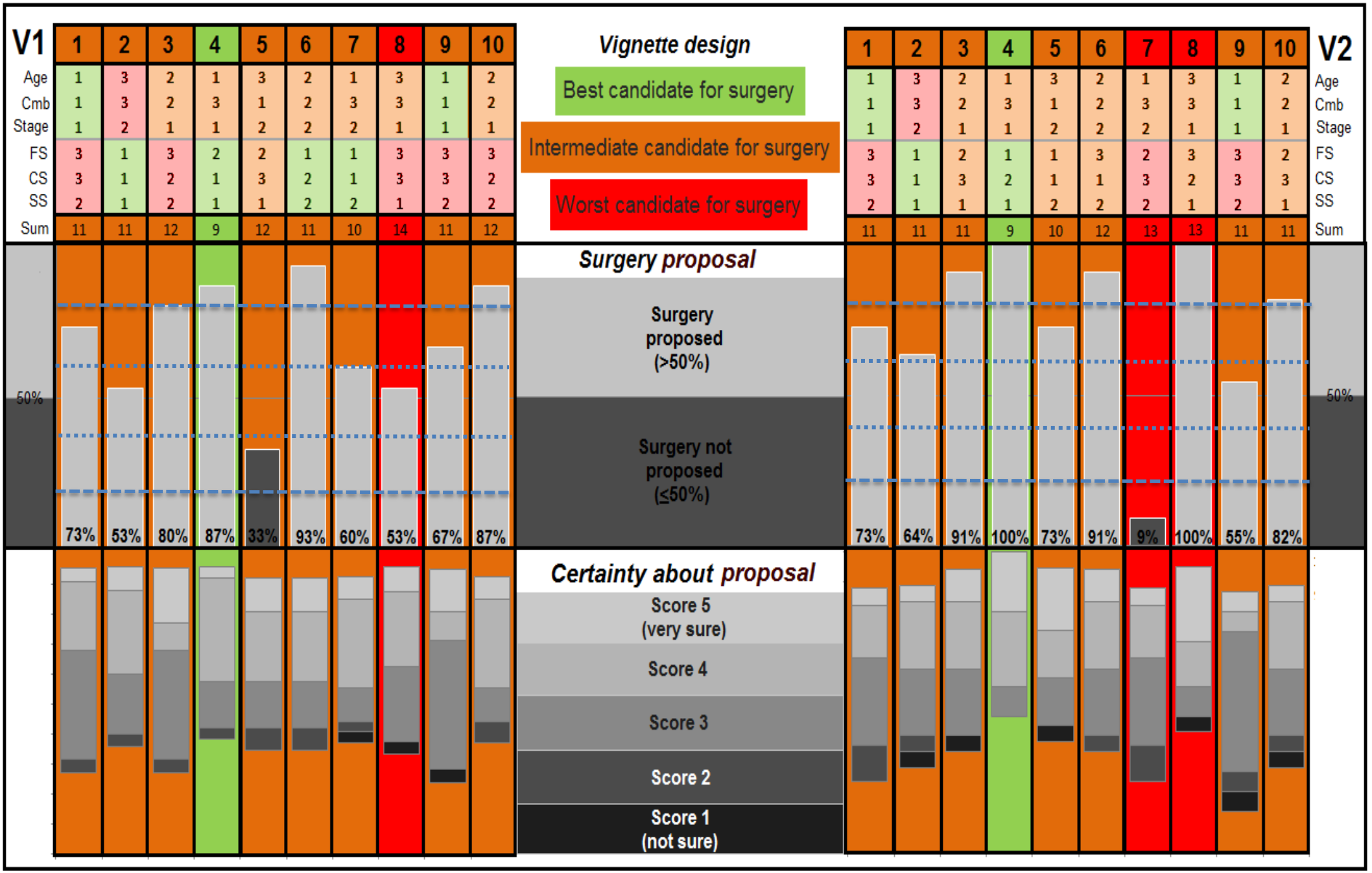


Figure 6. Overview of vignette designs, surgery proposals and certainty about these surgery proposals per vignette (1-10) per version

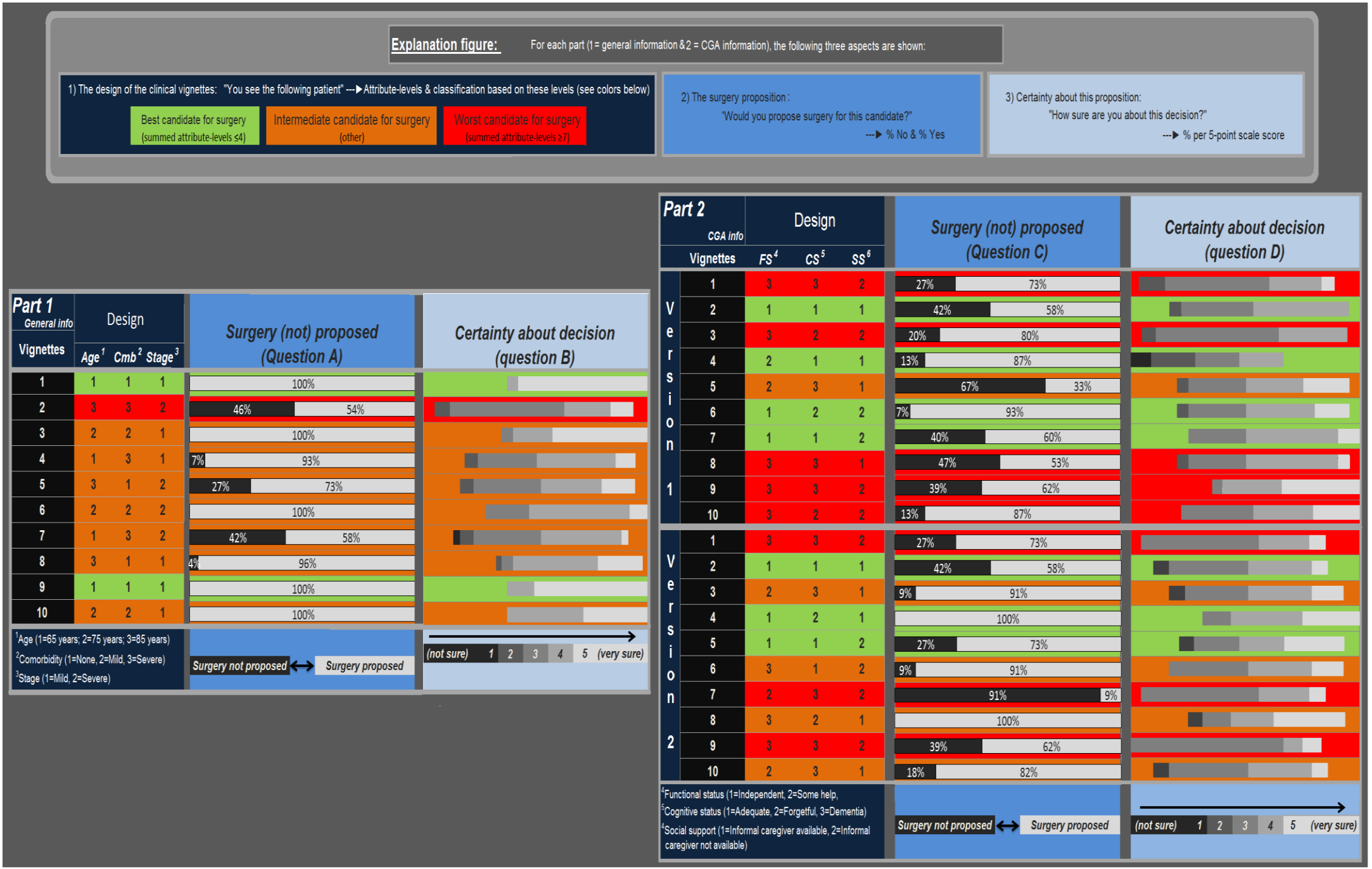


Figure 7. Overview of vignette designs, surgery proposals and certainty about these surgery proposals per vignette (1-10) per part (general info + CGA info)

EFFECTS OF ATTRIBUTE-LEVELS ON LIKELIHOOD OF RECEIVING SURGERY

The results of the logistic regression analysis between all dummy attribute levels and surgery choice based on all information are shown in table 6.

Ten cases had studentized residual bigger than ±2,5, which were kept in the analysis. The logistic regression model was statistically significant; $\chi^2(9) = 58{,}896$ ($p<0{,}0005$). The model explained 28,9% (Nagelkerke R^2) of the variance in surgery and correctly classified 76,2% of cases. Of the ten independent dummy variables four were statistically significant (italic in table 6). All B-coefficients were negative, indicating correct (dummy) coding of the dependent and independent variables, because the worse the vignette, the less chance of receiving surgery.

TABLE 6. LOGISTIC REGRESSION ANALYSIS & COEFFICIENT RANGE METHOD

Attribute	*Levels*	*B (Ext. Coeff.)*	*SE*	*P-value*	*Exp. (B) =OR*	*95% CI for Exp(B)=OR*		*Comparison of B-coefficient differences*			*Coefficient range method*	
						Lower	*Upper*	*Part-worth utilities per level*			*Range*	*%*
Age[1]	1	Reference						1	2	3	*3,368*	24%
	2	-1,310	0,884	0,139	0,270	0,048	1,527	-1,310	0	x		
	3	*-3,368*	*1,222*	*0,006*	*0,034*	*0,003*	*0,378*	*-3,368*	-2,058	0		
Cmb[2]	1	Reference						1	2	3	*3,459*	25%
	2	Due to redundancies, degrees of freedom have been reduced for this variable.										
	3	*-3,459*	*1,175*	*0,003*	*0,031*	*0,003*	*0,315*	*-3,459*	x	x		
Stage[3]	1	Reference						1		2	0,056	0,4%
	2	-0,056	0,802	0,945	0,946	0,197	4,552	-0,056		0		
FS[4]	1	Reference						1	2	3	1,642	12%
	2	-1,642	0,791	0,067	0,194	0,033	1,121	-1,642	0	x		
	3	-0,969	0,756	0,221	0,380	0,081	1,789	-0,969	0,673	0		
CS[5]	1	Reference						1	2	3	*2,527*	18 %
	2	-0,082	0,821	0,914	0,922	0,209	4,059	-0,082	0	x		
	3	*-2,527*	*1,164*	*0,002*	*0,080*	*0,016*	*0,399*	*-2,527*	-2,445	0		
SS[6]	1	Reference						1		2	*2,956*	21%
	2	*-2,956*	*1,862*	*0,011*	*0,052*	*0,005*	*0,509*	*-2,956*		0		
										Sum range	14,008	100,0%

[1]Age (1=65 years; 2=75 years; 3=85 years), [2]Comorbidity (1=None, 2=Mild, 3=Severe), [3]Stage (1=Mild, 2=Severe) [4]Functional status (1=Independent, 2=Some help, 3=Dependent), [5]Cognitive status (1=Adequate, 2=Forgetful, 3=Dementia), [6]Social support (1=Informal caregiver available, 2=Informal caregiver not available)

Best patients on each statistical significant attribute-level were at least 13 times more likely to receive surgery than worst patients (13 times for adequate cognitive status vs. dementia,

19 times for with social support vs. without social support, 29 times for age 65 vs. age 85 and 32 times for no comorbidity vs. severe comorbidity) [1].

Comparison of differences between (significant) coefficients per attribute showed that the influence of the difference between 85 years and 65 years on the surgery proposal was about the same as the difference between severe comorbidity and no comorbidity. Both these differences influenced the surgery proposal about twice as much as the difference between a dependent patient and an independent patient.

RELATIVE IMPORTANCE

The calculations and results of the coefficient range method and the relative importance of the attributes are shown in table 6.

Most important attributes, based on the range of part-worth utilities were comorbidity, age and social support (>20% of the total importance of attributes). Cancer stage had almost no importance in the surgery proposal compared to the other attributes. When the general information is compared to the CGA information, it could be seen that both are equally important (49% vs. 51%; see figure 8).

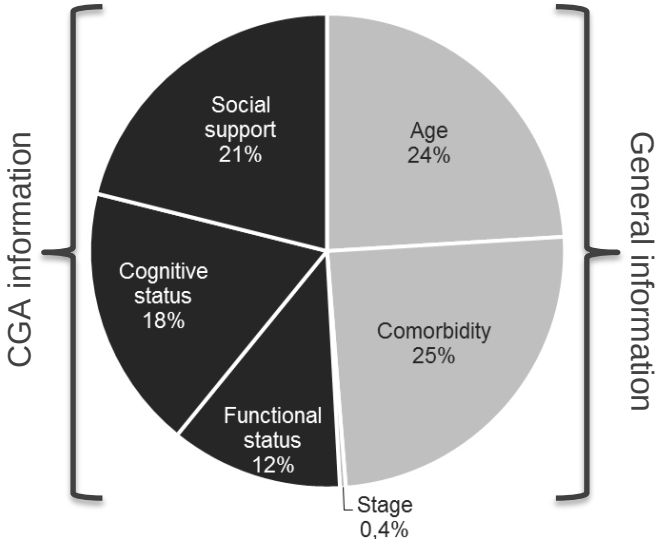


Figure 8. Relative importance of attributes

REQUESTED ADDITIONAL INFORMATION

Additional information requested by more than half of the respondents (>50%) was: changes in weight and nutrition state in the last 3 months, medication, risk of delirium, patient preferences and physical condition. Almost all respondents (>90%) requested the latter two.

[1] =1/Exp(b) = 1/OR, because of negative OR

DISCUSSION

SUMMARIZATION OF RESULTS

The aim of this study was to show how CGA results influence MDT members' surgery proposal for older CC patients. Results indicate that additional CGA information has little influence on the surgery proposal, because CGA information changed the surgery proposal in the minority of the chosen vignettes. However, the relative importance of general information and CGA information was similar. Mean certainty decreased after considering the additional CGA information and also in worst patient vignettes. Overall tendency to propose surgery was high and physicians agreed with each other in the majority of vignettes. Attributes that increased the likelihood of receiving surgery the most were comorbidity, age and social support.

EXPLANATION RESULTS AND COMPARISON WITH LITERATURE

SURGERY PROPOSALS AND OUTCOMES IN THE ELDERLY

In the clinical vignettes, the majority of patients received surgery according to the respondents, despite the "bad" attribute-levels presented in the vignettes. This is in line with the results of a large American retrospective study (1992-2005, 31.574 CC patients ≥ 80 years) (28) and a Spanish study (2006-2008, 950 CRC patients, all ages) (73), which both showed that the majority of patients received surgery (around 80%, even for elderly patients). These findings suggest that other findings of other studies that described decreased deployment of standard treatment for cancer in the elderly population due to the high (pre)frail incidence (5,21,22,23,73) mostly applies to non-surgical treatments such as chemotherapy and radiotherapy.

Because elderly are often excluded from clinical trials on which clinical practice guidelines are based, a distinction has to be made between the deployment of surgery as described above and the influence of surgery on the patient's outcomes. Therefore, looking at patient outcomes (like morbidity, mortality and surgery related complications which influence quality of life after surgery) specifically focused on elderly patient is needed. In a Dutch retrospective (2006-2008) study, 1924 patients with resections for stage I-II colorectal cancer were analyzed (74). 1-year mortality due to colon cancer after colon surgery increased with age, but this increase was not too substantial (less than 3% change from patients <65 years to patients ≥75 years). In an Italian retrospective (2004-2012) study, 446

colorectal cancer stage I-III patients were analyzed (75). Elderly patients suffered more from postoperative, late and systemic complications compared to younger patients. Like concluded from a systematic review on comparative outcomes of rectal cancer surgery between elderly and non-elderly, the level of evidence for most studies was weak (25). This emphasizes the need for high-quality clinical trials for the elderly.

Because of the current trends of an aging (Dutch) population and improved quality of life even at higher age (76), this need for better quality research focused on elderly becomes even more urgent. Furthermore, the definitions of “elderly” or “old” need to be revised because of these trends. Traditionally the starting age of elderly was the retirement age (i.e. 65 years) (1). In a survey amongst surgeons about the assessment and management of older cancer patients, SIOG found that only 12% would use 65 years as a cut-off point for defining a patient as old (77). About a third found 75 years a more appropriate age threshold and a quarter would even use 80 years. The biggest challenge thus with regard to defining the elderly will be to differentiate between biological and chronological age. Chronological age shouldn’t influence the surgery proposal, but other criteria that determine biological age (like comorbidities and physiological, functional and cognitive status) should be evaluated to differentiate between fit and frail elderly. The use of geriatric assessments has the potential to identify health issues that otherwise might not be known by the MDT. Therefore, inclusion of CGA results is recommended for the MDT.

CGA INFORMATION

Again, a distinction has to be made between the use of CGA results (like the actual deployment of surgery) and the influence of this use on the patient outcomes (like mortality and complications after surgery). The latter hasn’t been studied yet in randomized controlled trials (78). In this study, the use of CGA information (in part 2 of the vignettes) did not substantially influence the surgery proposal (physicians changed their proposal based on the additional CGA information in less than a fifth of the cases). Studies examining the influence of CGA before the start of the treatment on the final cancer treatment plan are scarce. In appendix 6, studies that analyzed this influence are shown (n=8). If CGA changed the final treatment proposal in these studies (n=6), CGA changed the treatment proposal in a higher proportion of patients than in this study. These different results can probably be attributed to the cancer types included and treatments that were focused on in the other studies. This study focused on whether to propose surgery or not for colon cancer

patients, because surgery is the golden standard. Without surgery, only palliative care remains for these patients ("milder" surgery is not an option). Most other studies focused on different types of cancer at the same time and the main focus was on chemotherapy modifications (like dose reductions). Furthermore, the other studies followed real patients and MDT's (pro- or retrospective), while this study used hypothetical vignettes. Because treatment plans are highly preference sensitive, the final treatment plan can deviate from the MDT proposal, which isn't taken into account in this study, but it is in the other studies.

Other studies into the proposal content of other MDT's showed medical dominance (focus on cancer pathology) (47,48), which assumes neglect of other information such as CGA information. However, this is not reflected in this study's results, because cancer stage showed to have negligible importance compared to the other attributes and the relative importance of CGA information was comparable to general information. Additional MDT visits could determine if this medical focus also exists in the MST and this study's results can serve as a notice for more awareness of CGA information.

COMPARISON WITH SIOG RECOMMENDATIONS AND IGZ INDICATORS FOR ELDERLY

The included attributes in the clinical vignettes are comparable to the focus of SIOG recommendations on frailty screening (79) and assessment and management (12,39,77) for older (colorectal) cancer patients. The focus of the IGZ indicators however is different (40); risk of delirium, risk of falling and malnutrition are important when assessing quality of care, but these hardly influence treatment proposals for physicians. Both are important for the patient, since both adequate treatment proposals and quality of care influence patient outcomes (80,81). Because of the complexity of the treatment proposal, included attributes only partially explain actual treatment proposals. This indicates that the results of this study should be seen within a broader range of considerations in the treatment proposal.

CLINICAL EYE

Evidence-based medicine (EBM), including standardized practice guidelines, protocols and checklists, was introduced in health care to reduce variations and improve efficiency, effectiveness, quality and safety in medical care (82). Application of EBM is difficult in the elderly population, since guidelines cover only a minority of the elderly population. Furthermore, medical decision-making, including proposing treatments, remains a complex process because many criteria need to be considered (83), which was also reflected in the

abundance of identified proposal-criteria in the first phase of this study (systematic literature review and interviews). Therefore, guidelines, protocols and check-lists can impinge on physicians' space to tailor care to individual patients (84). Physicians agreed in most clinical vignettes. Therefore, it could be argued that the clinical eye, which was also mentioned as an important, if not most important factor in the evaluation of patients, is sufficient for not evidence based cases, which call for individualized approaches. Because certainty decreased after seeing additional CGA information, the practical inclusion of CGA information in clinical reasoning, which is justified by the current study results, needs to be studied further (e.g. how to incorporate geriatric information or physicians focused on geriatrics in the MDT).

LIMITATIONS AND STRENGHTS

SELECTING ATTRIBUTE (-LEVELS)

A limitation in this study was the reliance on only one researcher in selecting articles and extracting results from these articles. Different interpretations of the articles' contents by different researchers could have been analyzed with Cohen's Kappa inter-rater reliability and it might have led to different rankings of the found proposal-criteria (85). By using the results of the systematic literature review as input and coding scheme for the interview, the "pink elephant" bias might have occurred; the tendency to see what is anticipated (86). Another limitation is the inclusion of a limited amount of attribute and attribute-levels (e.g. not all recommended topics by SIOG and IGZ were included). More attributes and attribute levels would have allowed more realistic simulation of actual multifaceted proposal, but because of response efficiency this wasn't desirable (57,65,66).

Important forgone considerations in this study were patient preferences and economic considerations. The omission of patient preferences in this CA (rationing: see chapter 2) is a serious limitation of this study, because treatment proposals are preference sensitive. Other CA studies also have omitted patient preferences (51 out of 52 included studies in a systematic review (87)) and therefore future research should incorporate this aspect to study the influence of patient preferences on the treatment proposal. Patient preferences were however recognized as important by all respondents, while economic considerations were neglected, which is a remarkable finding. In many other clinical vignette studies, costs also have been excluded (87). Because healthcare expenditures need to be contained, costs should be considered in treatment proposals like mentioned in the critical note by

Saltz about the questionable attainability and sustainability of current and future CRC care (88). Costs for colorectal cancer accounted for example for 0,7% of the total costs of Dutch health care in 2011, of which €234million were hospital costs (89). To reduce these costs, only fit elderly patients should be offered active treatment, while aggressive surgery should be neglected to frail elderly with limited life expectancies. These groups can be differentiated by performing CGA's (33,41).

SAMPLE SIZE AND RESPONDENTS

The most important limitation however, was the limited sample size. The response rate was moderate (47%), but other sample size guidelines recommend for example at least 300 respondents (min. 200) per group analysis (67). The small sample size reduced the statistical efficiency and this was reflected in the high p-values of the model estimates. Response quality however, was deemed high (good intra- and inter-reliability).

No opt-out possibility was given, because in real-life MDT members also don't have an opt-out option for treatment proposals. This however, implied that all respondents were forced to make a proposal, even if they weren't sure about their proposal. Certainty scores were never low, perhaps because of social desirability (physicians didn't want to admit that they weren't sure about a proposal they also could have been presented with in real-life). Especially for non-surgeons this could have led to inaccurate proposals, because in practice they don't make the final surgery proposal. Mean certainty without surgeons however still was high, which means that overall physicians were sure about their proposal. Because the sample size of this study was too low, no distinction could be made between profession types to demonstrate the lack of consensus and the diversity in treatment recommendation. Another clinical vignette study showed inconsistency between MDT members for stage I non-small cell lung cancer (90) and it is likely that this also occurs in colon cancer.

Further research with a bigger sample size and inclusion of other hospital MDT's could validate this pilot-study to find statistical significant results and to compare consistency in proposals between different professions. It would be interesting to study the differences between different physician groups (e.g. geriatricians and surgeons) and differences based on work experience (e.g. inexperienced and experienced physicians). Furthermore,

additional qualitative research about the results of this study could have been performed to better interpret the results.

STUDY FOCUS

The unexpectedly high surgery proposal for the worst dominant vignette indicated that the descriptions of vignettes could have been "worse", to really make the vignette dominant. However, the ISPOR CA guideline advises to exclude (too) dominant questions in the design, because these yield no information on trading-off proposal-criteria (66).

A final remark has to be placed about the focus of the study. Focus shifted from colorectal cancer in the first part (systematic literature review, explorative interviews) to colon cancer only in the second part (clinical vignette study). Therefore, incongruence between the first and second part might have occurred in terms of selected proposal-criteria and/or chosen treatment option. This shift also made it difficult to compare results of this study to other studies, in which colorectal cancer often is combined. Future research should look at the differences between both types of cancer and their proposals. Giving the same information in clinical vignettes for both patient groups, but varying the type of cancer could for example do this.

STRENGHTS

Strength of this study lies in the rigorous approach to elicit relevant proposal-criteria by combining results of 3 methods (systematic literature review, qualitative and quantitative clinical expert interviews). By doing this, inclusion of clinical relevant attributes and attribute-levels was assured, which enabled performing a clinical vignette study with relevant and reliable results. Furthermore, the steps of the ISPOR checklist for CA studies were followed and reported, resulting in an accurate and transparent study (presentation).

CONCLUSION

This study showed that overall proposal tended to favor surgery, even in (within the study) worst surgical candidates. Additional CGA information changed the surgery proposal in the minority of vignettes. However, uncertainty decreased if CGA information was added and also in intermediate and worst candidates. Therefore, additional CGA information should be considered in intermediate and worst surgical candidates (identified with geriatric screening tools). This enables making treatment proposals with more attention for elderly specific issues, which increases the quality of care for this older population.

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APPENDICES

APPENDIX 1. INTERVIEW PROTOCOL IN DUTCH

Interview MDT colorectale kanker

Datum: xx-xx-2016
Tijd: xx.xx u
Interviewer: Julia Keizer
Geïnterviewde: xxxx xxxx
Functie: xxxx xxxx

Voor het onderzoek van mijn master Health Sciences aan de Universiteit Twente houd ik interviews met leden van het multidisciplinair team colorectale kanker in het MST. Het interview zal mij helpen om in kaart te brengen hoe de behandeling van oudere (≥70 jaar) colorectale kankerpatiënten wordt bepaald en welke criteria hierbij een belangrijke rol spelen. Samen met de resultaten van een literatuurreview kan ik met deze interviews een goede vragenlijst opstellen. Het interview duurt ongeveer 20-30 minuten.

Voordat het interview gaat beginnen zou ik graag willen weten of ik het interview op mag nemen. Hierdoor kan ik het interview naderhand goed analyseren. De opname wordt na het analyseren verwijderd en antwoorden zijn nooit naar een persoon te herleiden. Stemt u hiermee in? (Opname starten)

Dan beginnen we nu aan het interview.

Kenmerken geïnterviewde
Functie:
Rol in het bepalen van de behandeling:

Behandelingsbeslissing bij oudere colorectale kankerpatiënten

Vraag 1) Zijn er behandelingsrichtlijnen specifiek voor oudere colorectale kankerpatiënten? (Afgekeurd addendum richtlijn CRC ouderen)

Vraag 2) Wat zijn redenen om oudere CRC patiënten niet of niet volgens de richtlijn te behandelen? (bijv. geen operatie, verminderde chemo dosis, etc.)

Vraag 3) Welke informatie heeft u minimaal nodig voor het bepalen van een behandeling bij nieuwe colorectale kankerpatiënten boven de 70?

Eerst zelf laten opnoemen wat de zorgverlener belangrijke informatie vindt.

Vraag 4) Welke aanvullende informatie zou de behandeling kunnen wijzigen? Dit kan bijvoorbeeld informatie zijn die nog niet wordt verzameld bij de patiënt of informatie die wel verzameld wordt, maar nog niet gebruikt wordt in de behandelbeslissing.

Vraag 5) Is leeftijd op zich een factor die mee zou moeten spelen in het bepalen van een behandeling voor colorectale kankerpatiënten?

Vraag 6) Bent u bekend met geriatrische assessments? Bijvoorbeeld in de vorm van de G8 of een Comprehensive Geriatric Assessment (CGA)?

*Evt. uitleg: De G8 vragenlijst wordt gebruikt als kwetsbaarheidsscreening in het MST en het richt zich bijvoorbeeld op **ondervoeding, mobiliteit, neuropsychologische problemen, polyfarmacie, algemene fitheid en leeftijd**. Mocht er uit deze test komen dat de patiënt kwetsbaar zou kunnen zijn, dan wordt de patiënt doorgestuurd naar de geriater die uitgebreidere testen uitvoert om aandachtsgebieden voor de oudere patiënt in kaart te brengen.*

Vraag 7) Welke informatie uit de geriatrische assessment neemt u mee in het bepalen van een behandeling voor colorectale kankerpatiënten?

Vraag 8) Welke toegevoegde waarde hebben dergelijke geriatrische assessments volgens u?

Vraag 9) Hoe weegt u de informatie uit een geriatrisch assessment af tegen de informatie over de patiënt die we aan het begin van het interview besproken hebben?

Vraag 10) Laten invullen SurveyMonkey.

Vraag 11) Zou het voor kunnen komen dat verschillende zorgverleners verschillende behandelingen zouden voorschrijven aan eenzelfde patiënt (voor dezelfde tumor) op basis van dezelfde informatie? Zo ja, waardoor zou dit verschil kunnen komen?

Dat was de laatste vraag. Heeft u nog opmerkingen of vragen?

Hartelijk bedankt voor uw medewerking. Mocht u nog vragen hebben, dan kunt u me altijd mailen (j.keizer@mst.nl of j.keizer@student.utwente.nl).

APPENDIX 2. CODING SCHEME

CGA Components (CGA)			
Functional status	**FS**	**Cognitive**	**C**
Cluster functional/physical	1	Cognition	1
Overall health	2	Dementia	2
Mobility	3	Vision/hearing	3
Treatment coping	4	**CGA**	**CGA**
Comorbidities	**Cmb**	Cluster geriatric	1
Cluster comorbidity	1	Frailty	2
Cardiac	2	**Psychological**	**Psych**
Pulmonary	3	Cluster psychological	1
Diabetic	4	Delirium	2
Atherosclerotic disease	5	**Emotional**	**Emot**
Peritoneal	6	Depression	1
Systemic	7	Cluster emotional status	2
Immune function	8	**ASA**	**ASA**
Physiologic	**Phys**	**Prognosis**	**Progn**
Cluster physiologic	1	Life expectancy	1
Renal function	2	Prognosis	2
Liver function	3	**Fatigue**	**Fati**
Sepsis	4	Cluster fatigue	1
Spontaneous bone fractures	5	Sleep deprivation	2
Anemia	6	**Falling**	**Fall**
Anaerobic threshold	7	**Family members'reports**	**Relexp**
Lifestyle	**LS**		
Nutrition	1		
Weight (+)	2	***Social support (SS)***	
Weight (-)	3	**Cluster social support**	**SS**
Alcohol/smoking/drugs	4	**Dependency**	**Dep**
Weight general	5	**Living situation**	**LivS**
Neglect and abuse	6	**Transportation**	**Trans**

Treatment characteristics (TC)	
Toxicity	**Tox**
Side-effects	1
Cluster toxicity	2
Complications	3
Uncomfortable feeling	4
Outcomes	**Outc**
Mortality/survival	1
QoL	2
Morbidity	3
Benefits	4
Efficacy	5
Cluster outcomes	6
Effectivity	7
Type of treatment	**ToT**
Emergency/elective	1
Treatment intent	2
Chemo (dosis)	3
Other treatment	**OT**
Polypharmacy	1
Surgery	2
Cluster previous treatment	3
Tolerability	**Tol**
Cluster tolerability	1
Resectability	2
Recurrence	**Rec**
Cluster recurrence	1
Convertible	2
Stoma needed	**Stoma**

Disease characteristics (DC)	
Stage	**Stage**
Metastasis	**Metas**
Location	**Loc**
Location	1
Cancer type	2
# of primaries	3
Imaging/histopathology findings	**Histo**
Tumor characteristics	1
CEA	2
Alkaline phosphate values	3
Markers	**Mark**
MSI	1
KRAS	2
Cluster markers	3
Infection	4
Other	5
Grade/differentiation	**Grade**
Symptoms	**Symp**
Bowel status	**BS**
Perforation/lesion	1
Gastrointestinal status	2
Obstruction	3
Presentation (synch/metachr, delayed)	**Pres**
Size	**Size**
Costs (C)	
Cluster costs	**Cost**
Insurance	**Ins**

Patient characteristics (PC)	
Age	**Age**
Gender	**Sex**
SES	**SES**
Cluster SES	1
Income	2
Geographic location	3
Marital status	**MS**
Race	**Race**
Preferences (P)	
Patient	**PP**
Preferences	1
Worries about time away from family	2
Worries about time away from work	3
Patient experiences	4
Family	**FP**
Physician factors (PF)	
Discretion	**PD**
Experience	**PE**
Evidence based	**EB**
Practice characteristics	**PC**

APPENDIX 3. OVERVIEW QUESTIONNAIRE AND CODING IN SPSS

Section	Question code	Question	Answer options coded in SPSS	Analysis	Result
1: Respondent characteristics	RC1	Gender	Categorical (1; male, 2; female)	Count answer options	Ratio (%) female/male
	RC2	Age	Continuous (scale)	Mean (SD) + min/max	Age
	RC3	Function	Categorical	Count answer options	Ratio (%) type of profession
		RC31	(1; surgeon)		
		RC32	(2; case manager)		
		RC33	(3; geriatrician)		
		RC34	(4; medical oncologist)		
		RC35	(5; gastroenterologist)		
		RC36	(6; radiotherapist)		
		RC37	(7; nurse)		
		Other	(8; other)		
	RC4	Work experience	Continuous (scale)	Mean (SD) + min/max	Experience respondents
	RC5	New seen CRC patients/month	Continuous (scale)		
2: Vignettes 1+2	P1Q1/2	Part 1/2 question 1 & 3	Categorical (1; No, 2; Yes)	Count answer options	Extreme vignettes --> exclusion criterion
	P2Q3/4				
2: Vignettes 3-8	P1Q1/2			Median + upper/lower limit	Diversity in answers to vignettes.
	P2Q3/4				
2: Vignettes 9+10	P1Q1/2	Part 1/2 question 2 & 4	Scale (1: Not sure – 5: Very sure)	Intraclass correlation (ICC)	Consistency answers (vignettes 1-9 & 3-10)
	P2Q3/4				
2: Vignettes 1-10	P1Q1/2	Part 1/2 question 1 & 3	Categorical (1; No, 2; Yes)	Descriptive statistics	Overall proposal tendencies, difference between part 1 and part 2 proposals + chance that patient receives surgery + relative importance attribute (-levels)
2: Vignettes 1-10	P2Q3/4	Part 1/2 question 2 & 4	Scale (1: Not sure – 5: Very sure)	Logistic regression (binomial) + Coefficient range method	
3: Additional information	AQ3	Additional information	Categorical	Count answer options	Additional information requested by more than half of the respondents
		1	Weight/nutritional state (last 3 months)		
		2	Lifestyle		
		3	Gender		
		4	Medication		
		5	Risk of falling		
		6	Emotional status		
		7	Risk of delirium		
		8	Fatigue		
		9	Patient preferences		
		10	Family preferences		
		11	Physical condition		
		Other	Other		

APPENDIX 4. ATTRIBUTES AND ATTRIBUTE-LEVELS

AGE

"The elderly" or "older patients" isn't a predefined category with a fixed starting age. In the literature there is quite some discussion about its definition (see for example (1)). In the systematic literature review most studies agreed that chronological age on its own shouldn't prevail in treatment proposals, but it needs to be considered together with other criteria. The interview respondents were more divided on this subject; some agreed with the literature and others were against treating the oldest older patients (>80 years) at all. The SIOG recommended that all patients of 65 and above should undergo a preoperative evaluation (9), so this was taken as the lowest level. To get an equally distribution in the age levels, a 10 year increase per level was used.

COMORBIDITIES

Like cancer incidence, comorbidity incidence rises with advancing age (91,92). Comorbidity negatively influences patients in several ways. Patients with comorbidities have shown to receive less standard cancer care and the chance of completing the full treatment is lower compared to patients without comorbidities. Furthermore, mortality and postoperative complications are higher in patients with comorbidities (91,93,94,95). Cardiovascular, diabetic and pulmonary comorbidities are the most common comorbidities in the elderly population (92,96,97,98). Therefore, the attribute-levels were varied in comorbidity severity, using these three diseases.

CANCER STAGE

Without information on the type and severity of cancer, no treatment plan can be determined. To discriminate between relatively mild disease and relatively severe disease, a medical oncologist and a gastrointestinal surgeon made descriptions for curable and advanced cancer stages, mainly focusing on the presence of distant metastasis, because this determines the prognosis of the patient.

FUNCTIONAL STATUS

Functional decline and reduced reserve capacity to compensate for this decline contribute to increased risks to the treatment and treatment outcomes of older patients (98). Different tools exist to measure functional status and a commonly used tool is the Katz-activities-of-daily-living (KATZ-ADL). It measures patients' dependency on several basic daily

activities, like bathing, dressing and feeding. It is one of the oldest indices for measuring ADL, it is used in many practices, including in the MST and it has proven to be useful in creating a common language about the functional status of patients (99). Therefore, elements of the KATZ-ADL were used to incrementally describe the levels of functional status.

COGNITIVE STATUS

Cognitive status influences treatment proposal capacity and cognitive impairment is associated with postoperative delirium. Furthermore, dementia is associated with increased perioperative mortality and postoperative adverse outcomes (100,101). Cognitive status is often measured in research with the Folstein mini-mental status examination (MMSE) (102,103). This tool consists of several questions and exercises to be answered/performed by the patient and points are scored with correct answers/actions (so the higher the score, the better). The frequently named cut-off score of 24 points for dementia (104) was used as a reference point for the level descriptions in this study. A slightly forgetful patient is scored above the cut-score and a patient with mild dementia is scored below the cut-score.

SOCIAL SUPPORT

(Perceived) social support plays an important role before, during and after cancer treatment, not only because of emotional support, but also because of practical care giving support (105,106,107,108,109). Because discriminating between the presence/absence of social support in three levels could be confusing (a bit social support is too vague), only two levels were presented to make a clear distinction between available social support and the lack of social support.

APPENDIX 5. CONSISTENCY IN ANSWERS BETWEEN VIGNETTES 1-9 & 3-10

Ranks

Parts	Questions A-D		N	Mean Rank	Sum of Ranks	Conclusion
Part 1: general information	Question A: Surgery choice Part 1 (vignette 9) - Surgery choice Part 1 (vignette 1)	Negative Ranks	0	,00	,00	No change
		Positive Ranks	0	,00	,00	
		Ties	26			
		Total	26			
	Question B: How certain Part 1 (vignette 9) - How certain Part 1 (vignette 1)	Negative Ranks	3	2,00	6,00	3 respondents were less certain about their choice in vignette 9
		Positive Ranks	0	,00	,00	
		Ties	23			
		Total	26			
Part 2: CGA information	Question C: Surgery choice Part 2 (vignette 9) - Surgery choice Part 2 (vignette 1)	Negative Ranks	4	3,00	12,00	4 respondents changed from yes to no and 1 respondent changed from no to yes
		Positive Ranks	1	3,00	3,00	
		Ties	21			
		Total	26			
	Question D: How certain Part 2 (vignette 9) - How certain Part 2 (vignette 1)	Negative Ranks	5	6,10	30,50	5 respondents were less certain about their choice in vignette 9, while 5 were more certain
		Positive Ranks	5	4,90	24,50	
		Ties	16			
		Total	26			

Test Statistics[a]

	Question A	Question B	Question C	Question D	Conclusion
Z	,000[b]	-1,732[c]	-1,342[c]	-,318[c]	No statistical significant differences were found
Asymp. Sig. (2-tailed)	1,000	,083	,180	,751	

a. Wilcoxon Signed Ranks Test
b. The sum of negative ranks equals the sum of positive ranks.
c. Based on positive ranks.

Ranks

Parts	Questions		N	Mean Rank	Sum of Ranks	Conclusion
Part 1: general information	Question A: Surgery choice Part 1 (vignette 10)- Surgery choice Part 1 (vignette 3)	Negative Ranks	0	,00	,00	No change
		Positive Ranks	0	,00	,00	
		Ties	26			
		Total	26			
	Question B: How certain Part 1 (vignette 10) - How certain Part 1 (vignette 3)	Negative Ranks	5	4,00	20,00	5 respondents were less certain about their choice in vignette 10, while 2 were more certain
		Positive Ranks	2	4,00	8,00	
		Ties	19			
		Total	26			
Part 2: CGA information	Question C: Surgery choice Part 2 (vignette 10) - Surgery choice Part 2 (vignette 3)	Negative Ranks	1	1,50	1,50	1 respondent changed from yes to no and 1 respondent changed from no to yes
		Positive Ranks	1	1,50	1,50	
		Ties	24			
		Total	26			
	Question D: How certain Part 2 (vignette 10)- How certain Part 2 (vignette 3)	Negative Ranks	8	8,44	67,50	8 respondents were less certain about their choice in vignette 10, while 7 were more certain
		Positive Ranks	7	7,50	52,50	
		Ties	11			
		Total	26			

Test Statistics[a]

	Question A	Question B	Question C	Question D	Conclusion
Z	,000[b]	-1,134[c]	,000[b]	-,471[c]	No statistical significant differences were found
Asymp. Sig. (2-tailed)	1,000	,257	1,000	,637	

a. Wilcoxon Signed Ranks Test; b. The sum of negative ranks equals the sum of positive ranks; c. Based on positive ranks

APPENDIX 6. STUDIES ON THE IMPACT OF GERIATRIC ASSESSMENTS ON CANCER TREATMENT MODIFICATION

Study author and publication year	Type of study	Type of cancer	Sample size	% of patients with treatment modification as a result of the geriatric assessment	Modification on treatment
Girre et al., 2008 (54)	Pro-spective	Solid malignancies, different stages	93	39% (n=36)	Chemo dose modifications and surgery rejection
Marenco et al., 2008 (110)	Pro-spective	Solid malignancies, different stages	571	49% (n=214)	Active vs. palliative treatment
Caillet et al., 2011 (111)	Pro-spective	Mixed cancer types and stages	375	21% (n=78)	Decreased chemo intensity, rejection of surgery
Chaibi et al., 2011 (53)	Pro-spective	Solid malignancies, different stages	161	49% (n=79)	Delayed vs. less/more intensive chemotherapy
Aparicio et al., 2011 (56)	Pro-spective	Digestive cancers, different stages	21	Cancer treatment not modified	Chemotherapy dose reduction and rejection of surgery in patients which received chemotherapy and/or radiotherapy
Barthélémy et al., 2011 (55)	Retro-spective	Breast cancer, different stages	192	Cancer treatment not modified	Receiving adjuvant chemo-therapy
Horgan et al., 2012 (112)	Pro-spective	Lung and gastrointestinal, locally advanced or metastatic disease	30	20% (n=6)	“Watch and wait” policy
Kenis et al., 2013 (41)	Pro-spective	Mixed cancer types and stages	1115	25% (n=282)	Not defined

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