A difficult balancing act : Informing breast cancer patients about adjuvant systemic therapy

Engelhardt, E.M.G.

Chapter 7

Disclosing the uncertainty associated with prognostic estimates in breast cancer: *current practices and patients' perceptions of uncertainty*

Ellen G. Engelhardt
Arwen H. Pieterse
Paul K.J. Han
Nanny van Duijn-Bakker
Frans Cluitmans
Ed Maartense
Monique MEM Bos
Nir I. Weijl
Cornelis J.A. Punt
Patricia Quarles van Ufford-Mannesse
Harm Sleeboom
Johanneke EA Portielje
Koos JM van der Hoeven
F.J. Sherida Woei-A-Jin
Judith R. Kroep
Hanneke CJM de Haes
Ellen M.A. Smets
Anne M. Stiggelbout

Medical Decision Making (2017) 37: 179-192

Abstract

Background

Treatment decision-making is often guided by evidence-based probabilities, which may be presented to patients during consultations. These probabilities are intrinsically imperfect, and embody two types of uncertainties: aleatory uncertainty arising from the unpredictability of future events, and epistemic uncertainty arising from limitations in the reliability and accuracy of probability estimates. Risk communication experts have recommended disclosing uncertainty. We examined whether uncertainty was discussed during cancer consultations, and whether and how patients perceived uncertainty.

Methods

Consecutive patient consultations with medical oncologists discussing adjuvant treatment in early-stage breast cancer were audiotaped, transcribed, and coded. Patients were interviewed after the consultation to gain insight into their perceptions of uncertainty.

Results

In total 198 patients were included by 27 oncologists. Uncertainty was disclosed in 49% (97/197) of consultations. In those 97 consultations, 23 allusions to epistemic uncertainty were made and 84 allusions to aleatory uncertainty. Overall, the allusions to the precision of the probabilities were somewhat ambiguous. Interviewed patients mainly referred to aleatory uncertainty if not prompted about epistemic uncertainty. Even when specifically asked about epistemic uncertainty, one in four utterances referred to aleatory uncertainty. When talking about epistemic uncertainty many patients contradicted themselves. In addition, one in ten patients seemed not to realize that the probabilities communicated during the consultation are imperfect.

Conclusions

Uncertainty is conveyed in only half of patient consultations. When uncertainty is communicated, oncologists mainly refer to aleatory uncertainty. This is also the type of uncertainty that most patients perceive and seem comfortable discussing. Given that it is increasingly common for clinicians to discuss outcome probabilities with their patients, guidance on whether and how to best communicate uncertainty is urgently needed.

Introduction

Medical decision-making, whether relating to diagnostic procedures or treatment, should ideally be guided by evidence-based probabilities. Numerous prediction models have been developed to promote this goal. The individualized prognostic estimates these models provide facilitate better conceptualization of the trade-offs between benefit and harm of different treatment options. However, even evidence-based probability estimates are intrinsically imperfect. They are based on past observations and unavoidably limited evidence, resulting in two major types of uncertainty. First-order, or *aleatory uncertainty,* arises from the unpredictability of single events arising from the fundamental indeterminacy or randomness of future outcomes. Aleatory uncertainty is inherent to the *concept* of probability (we seldom speak of a probability of 1 or of 0). Second-order, or *epistemic uncertainty*, arises from deficits in knowledge, due to limitations in a) the precision of the risk estimates or b) their applicability to a specific patient (1, 2).

Risk communication experts have argued, mainly from an ethical perspective, that patients should be fully informed, and thus also be informed about these uncertainties (3). Failure to explicitly address epistemic and aleatory uncertainties may create misconceptions about the level of precision and individualization of probabilities presented during consultations. In the absence of adequate communication of such uncertainty, patients may have excessive confidence in probabilities, thus (potentially) resulting in pseudo-certainty.

Currently, no literature is available on the extent to which physicians communicate the epistemic uncertainty of prognostic estimates and the inability to predict individual disease outcomes. In addition, it is unknown to which extent patients understand these uncertainties and how these uncertainties are best communicated (3, 4). Clinicians may be hesitant to communicate uncertainty, fearing that such communication would make the information (even) more difficult for patients to comprehend, for we know that most people struggle to understand probabilities, irrespective of their education level (1, 5). For clinicians it is a challenge to find a balance between ´fully´ informing their patient, whilst not overwhelming them by providing too much information.

In the current study, we investigated the communication of uncertainty in the context of decision-making about adjuvant systemic treatment for early-stage breast cancer. Stage I-III breast cancer patients undergoing adjuvant systemic treatment may experience improvement in both disease-free and cancer-specific survival (6-10). Using known clinical prognosticators (e.g., tumor size, nodal status and differentiation grade) and/or bio-molecular profiles, the likelihood of beneficial treatment outcomes can be

calculated, for instance using the Adjuvant! prediction model (11). The likelihoods from Adjuvant! are frequently discussed during consultations in the adjuvant setting (12, 13). In combination with estimates of treatment effect, these likelihoods improve insight on the balance between the potential benefits and side-effects of treatment (10, 14, 15). We assessed a) *whether* and *which type* of uncertainty oncologists disclosed: i.e., the limitations in the precision of risk estimates/their applicability to an individual patient and/or unpredictability of single events, and b) patients' perceptions of the uncertainty associated with probabilities discussed during the consultation.

Methods

Design

Patient sample

The current study was nested in a large multicenter observational study with a participation rate of 358/500 (72%), which assessed the communication of survival probability estimates calculated by the Adjuvant! prediction model (11) during consultations of stage I-III invasive breast cancer patients by medical oncologists. Consecutive outpatient female breast cancer patients, eligible to receive chemotherapy and/or endocrine therapy, who were fluent in the Dutch language, were invited to participate in the current study. We included patients if survival probabilities from the Adjuvant! prediction model had been discussed during the consultation (Figure 1). This was determined following analysis of the content of the consultations. The medical ethics boards of the participating hospitals approved the study.

Adjuvant! prediction model

Adjuvant! (11) is a freely available online prognostication tool that provides estimates of 10-year a) overall, b) breast cancer-specific, and c) disease-free mortality and d) benefit of adjuvant systemic treatment. The information is presented as bar charts. Adjuvant!'s prognostic estimates are based on patient and tumor characteristics (i.e., age, patient's general health, tumor size, nodal status, estrogen receptor status and histological tumor grade) and type of systemic treatment. Oncologists may print the page to hand to the patient, or show the results on a computer screen.

Procedures

Consultations

Prior to their consultation, patients were informed that the study aimed to investigate information provision during consultations concerning adjuvant systemic therapy. The concept of uncertainty was not introduced. Oncologists were instructed to conduct their consultation as usual. Consultations were audiotaped after patients had given written informed consent.

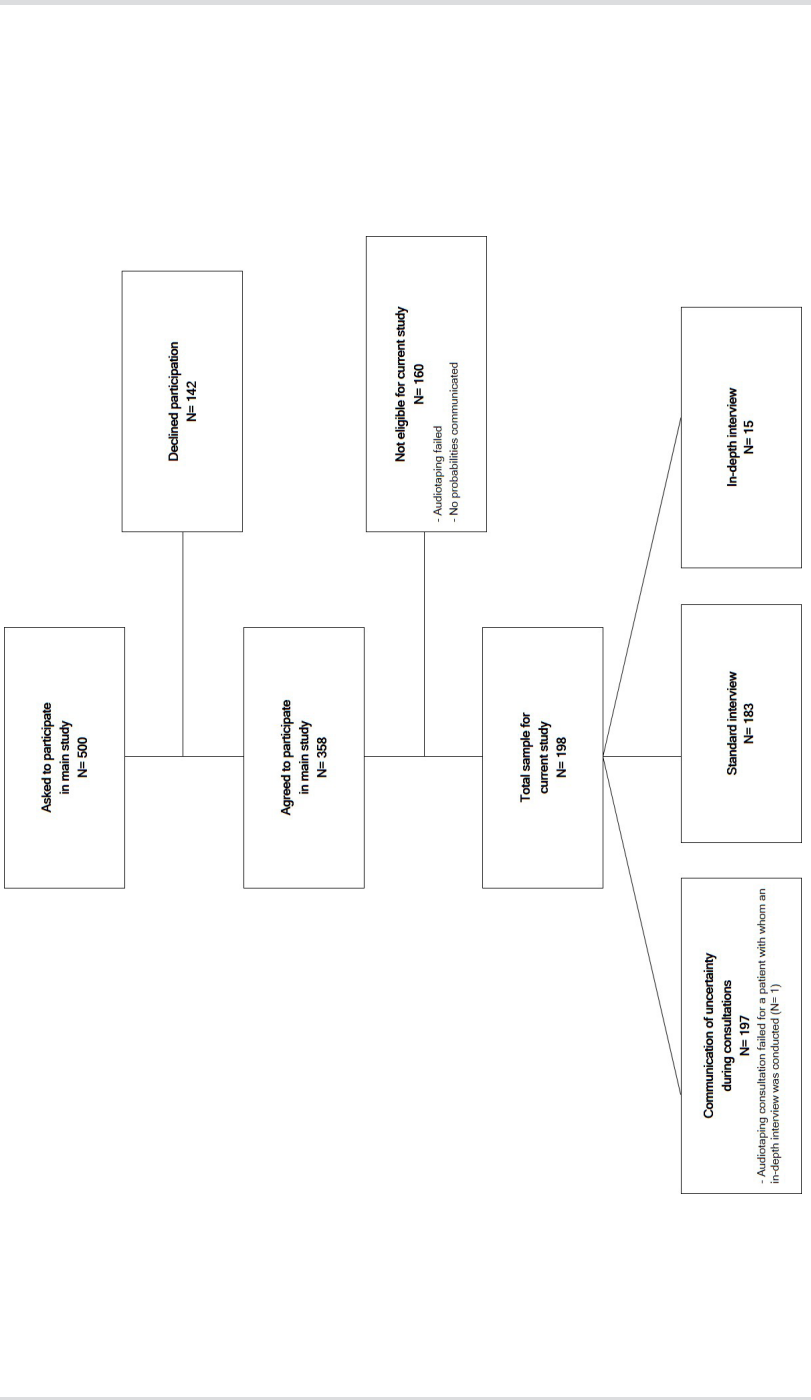

Figure 1 Flow chart of patient recruitment.

Patient interviews

Uncertainty was addressed in two types of interviews, 1) 'Standard' and 2) 'In-depth' interviews. The standard interview was a component of the main study. Patients were interviewed by telephone within seven days of their consultation (mean=3.4 days). The interviewer had no knowledge of what had been discussed during the consultation prior to this interview. Given the extensive character of the interview of the main study, we chose to only probe about epistemic uncertainty, since this is particularly relevant in the context of risk communication using probabilities from prediction models. To begin with, we asked patients whether the oncologist had discussed probabilities during the consultation. If patients indicated that this was the case, we asked them to list the probabilities discussed. Next, we posed two probes on uncertainty. First, we posed an 'Open probe': "*What do the probabilities [repeat probabilities the patient has already mentioned] mean to you?*". Second, we posed a 'Precision probe': "*In your opinion, are the probabilities you were provided with during the consultation [repeat probabilities the patient has already mentioned] exact survival probabilities… [pause] or could they be higher or lower for example*".

As probing turned out to be a challenge, not only practically but also ethically, with limited time, we could not elaborate on uncertainty during the standard interviews. Therefore, we decided to conduct additional in-depth interviews solely dedicated to uncertainty in a subset of patients not previously interviewed. Thus, we hoped to achieve a more comprehensive exploration of the patients' awareness of and views on epistemic uncertainty (consisting of the imprecision of risk estimates and their applicability to an individual patient), and the unpredictability of single events (i.e. aleatory uncertainty). We extended the inclusion period of the main study to recruit patients for these latter interviews. Expecting to need at least 15 interviews to reach saturation, we approached 15 consecutive patients not previously interviewed with whom probabilities had been discussed during the consultation. We conducted the in-depth interview only if patients indicated that probabilities had been discussed, irrespective of whether this had indeed been the case (according to the audiotapes). After 12 in-depth interviews, no new themes had emerged. Consequently, we ended inclusion and completed three already scheduled interviews.

On average, in-depth interviews took place within four days of the consultation (range: 0-12 days), either in person (N=10) or, by telephone if preferred (N=5). We recruited and informed patients in the same way about the study as the patients of the standard interviews. First, we used an '*Open probe*' not introducing the concept of uncertainty, to assess whether patients spontaneously referred to the uncertainty associated with the probabilities. Thereafter, we probed patients' perception of the uncertainty associated with the survival probabilities discussed during the consultation. We also asked patients whether - to the best of their recollection - uncertainty had been discussed

during the consultation and whether they thought it important to hear about such uncertainty during the consultation (see Appendix A for the probes on uncertainty used in the in-depth interviews).

Table 1 Patients and consultation characteristics (N (%))

	Overall N=198	Standard interview sample N=183	In-depth interview sample* N=15
Mean age in years (range)	59 (32-90)	59 (32-90)	54 (37-73)
Recruited at			
Academic medical center	52 (26)	47 (26)	5
General teaching hospital	146 (74)	136 (74)	10
Education			
Low	30 (19)	27 (19)	3
Intermediate	82 (52)	78 (54)	4
High	45 (29)	40 (28)	5
Missing	41	38	3
Numeracy			
Low	33 (21)	31 (21)	2
Intermediate	42 (26)	39 (27)	3
High	84 (53)	77 (52)	7
Missing	39	36	3
Median duration of consultation in minutes (range)	28 (5-80)	28 (5-80)	27 (17-62)
Treatment discussed			
Chemotherapy	21 (11)	19 (10)	2
Endocrine therapy	21 (11)	20 (11)	1
Both	156 (79)	144 (79)	12

* For one patient with whom we conducted an in-depth interview, audiotaping of the consultation failed.

Patient and oncologist questionnaire

Patients completed a written survey after having been interviewed assessing age and education level (defined using the highest level of schooling/vocational training completed) as well as objective numeracy, i.e., their ability to understand and use numbers. We used the seven expanded numeracy items proposed by Lipkus *et al.* (5). Scores (range: 0-7) were divided into three categories (low numeracy= 0-2; intermediate numeracy= 3-5; high numeracy= 6-7).

After patient recruitment was closed, we asked oncologists to fill out a survey to obtain their age, gender, and number of years of experience with the systemic treatment of breast cancer. They were also asked to indicate their reluctance to disclose uncertainty

to patients on the relevant subscale of the Physicians' Reactions to Uncertainty Scale (example of items: "*When physicians are uncertain of a diagnosis, they should share this information with their patients*", and "*If I shared all of my uncertainties with my patients, they would lose confidence in me*") (16) (scored on a six-point Likert scale, range between 5-30, with higher scores indicating greater reluctance towards disclosure). Finally, we asked oncologists to indicate the frequency with which during consultations they discussed epistemic and aleatory uncertainty with patients on five-point Likert scales (categories: never, seldom, sometimes, often, and always).

Coding and analyses

Consultations

Two trained researchers analyzed the content of the consultations to ascertain which treatment had been discussed (chemotherapy, endocrine therapy or both) and identify references to epistemic (yes/no) and aleatory uncertainty (yes/no).

Due to time constraints, it proved impossible to transcribe all consultations. Therefore, consultations were analyzed either directly from a verbatim transcription (N=94/197 (48%)) or from audio (N=103/197 (52%)). The coders first coded ten transcripts independently. Inter-rater agreement was 100%. To also ensure the reliability of coding directly from audio, each coder coded a sample of consultations (N=13-16) that had already been coded from transcript minimally three months after the original coding. The agreement between coding from audio and transcripts was again high (81% and 83%, respectively). As the agreement between coders was good, one researcher performed final coding.

Patient interviews

Patients' answers to the uncertainty probes in the Standard Interviews were transcribed. To categorize emerging themes, the research team developed an initial codebook based on the literature and open coding by two researchers of a subset of five consultations, thereafter it was refined and applied. This process was repeated several times, and the categories in the codebook are based on the coding of a subset of 30 interviews. The content of all standard interviews was double-coded by two trained researchers independently, and discrepancies were resolved in consensus meetings.

All 15 in-depth interviews were transcribed verbatim and coded independently by the two trained researchers, using the same categories used to code the standard interviews as a starting point. New categories were added as encountered. Discrepancies were resolved in consensus meetings.

Table 2 Oncologist characteristics (N=18)	
	N (%)
Median age in years (range)	42 (30-66)
Missing	7
Gender (male)	12 (44)
Experience with breast cancer systemic treatment (in years)	
≤ 5	9 (45)
6-10	2 (10)
>10	9 (45)
Missing	7
Oncologists' reluctance to disclose uncertainty to patients (median (range))*	13 (5-17)
Missing	7
Self-reported frequency of disclosure of uncertainty (% often and always)	15 (79)
Aleatory uncertainty (i.e., the unpredictability of single events)	
Epistemic uncertainty, specifically:	
precision of prognostic estimates	9 (47)
applicability to an individual	8 (42)
Missing	8

* Five-item reluctance to disclose uncertainty to patients subscale of the Physicians' Reactions to Uncertainty Scale (16), scored on a six-point Likert scale; the higher the score, the greater the reluctance towards disclosing uncertainty to patients (score range: 5-30).

Finally, the two coders independently grouped the 40 categories (i.e., themes) identified during the coding of both the standard and in-depth interviews into overarching domains for presentation purposes. The definitive grouping was established through further discussion and consensus among members of the research team (see Table 3 for the Standard Interview themes and Figure 2 for the In-depth Interview domains).

Results

We included 198 patients (Mdn age =59 years; range: 32-90). Overall, 74% of patients were recruited at general teaching hospitals, 29% were highly educated, and 53% were highly numerate (Table 1). The median duration of the consultations was 28 minutes (range: 5-80). Audiotaping of the consultation was successful for all patients except one. In 79% of consultations Adjuvant!'s prognostic estimates were presented orally and its output was displayed visually on the computer screen and/or on a printout of the output. The standard interview was conducted with 170 of the 198 patients, the in-depth interview was conducted with 15 patients, and no interview was conducted with 13 patients (nine patients could not be reached by telephone within 1 week after the consultation, and four declined to be interviewed).

Twenty-seven medical oncologists (Mdn age = 42 years; range: 30-66) recruited patients (Mdn=7 patients per oncologist; range: 1-33) (Table 2). Twenty oncologists (partially) completed the survey (74%), of whom 12 had more than 10 years of experience in this setting. Oncologists showed low to moderate reluctance towards disclosing uncertainty to patients (Mdn=12 out of a maximum of 30 points; range: 5-17). Nine of the 19 oncologists said they often or always discuss epistemic uncertainty (i.e. the imprecision of risk estimates and/or their applicability to a specific patient) during consultations, and 15/19 said they often or always discuss the unpredictability of single events.

Consultations

Disclosure of uncertainty during consultations

In about half (N=97/197 (49%)) of the consultations some type of uncertainty was disclosed. During these consultations, 107 references to uncertainty were made, of which 84 (79%) allusions to the unpredictability of single events (aleatory uncertainty). For example, one oncologist said: *"… [there are] no guarantees. It remains … I always say that in reality if you look at an individual it is 100% or 0%. So you either get the disease back or you don't, right. But if you have 100 women, then you have 30 women in whom during the course of 10 years, metastases will manifest... And I can't tell just by looking at you whether you are one of the 70 lucky ones or one of the 30 unlucky ones".* The remaining 23 (21%) references to uncertainty were allusions to the imprecision of the risk estimates and/or their applicability to a specific patient (epistemic uncertainty). Allusions to the imprecision of the risk estimates were generally somewhat vague, for example: *"Of course there always is a margin associated with such statistics"*. Utterances about the applicability of the probabilities to specific (subgroups of) patients were more tangible, for example: "*… look these are averages … yes. It's a large database, and we can't comment on the individual ... the only thing we can do is look at averages. And of course, there are always exceptions on both sides*", or "*… these probabilities will be somewhat different for you … your relapse risk will be higher, because the model*

[Adjuvant!] does not take the Her2 [Her2neu receptor status] into account".

Standard interviews

Patients' perception of the various types of uncertainty

One hundred forty-four (85%) patients indicated that probabilities had been discussed during the consultation. We posed the open probe to them. Of those 144 patients, 97 (67%) did not make a reference to uncertainty and 47 did. The response to the open probe of 12 of these 47 patients contained allusions to more than one aspect of uncertainty, resulting in 62 allusions. Overall, 37/62 allusions were about the unpredictability of single events, and 10/62 allusions were about the imprecision of the risk estimates or their applicability to a specific patient. The remaining 15/62 allusions were general statements without further clarification as to what the patient was aiming at (e.g., "*It's just statistics …*" or "*… it's statistically a substantial reduction of my recurrence risk*") or statements about the patients' struggle to cope with uncertainty. Table 3 presents patients' utterances about uncertainty during the standard interview.

Understanding of imprecision

The imprecision probe was posed to 80% (115/144) of patients who indicated probabilities had been communicated. This probe was not posed to 29 patients as the interviewer felt they were too emotional and/or had too limited understanding of the probabilities to allow probing. We found that patients generally seemed to struggle with what we were asking them. Patients seemed to think that we were asking them whether the probabilities they had heard during the consultation were correct, e.g., "*I think they calculated that [the probabilities] correctly. Yes, I'm confident about that*". Fifteen out of the 115 patients (13%) indicated they were unable to provide an answer. The 100 patients that did provide an answer made 178 allusions to uncertainty (Table 3). We were asking patients about the imprecision of the risk estimates, yet only 35% (63/178) of utterances referred to imprecision.

One out of three patients who alluded to imprecision (20/63) indicated that the probabilities were exact, i.e., they reported no uncertainty about the probability. About one out of four (41/178) utterances were an allusion to the inapplicability of probabilities to an individual, and 23% (41/178) of utterances were an allusion to the unpredictability of single events. The remaining 26 of the 178 (15%) remarks were statements about patients' struggle to cope with uncertainty or vague allusions to uncertainty (e.g., "*… it's just statistics*").

In-depth interviews

Figure 1 provides an overview of the themes identified in the 15 in-depth interviews (see Table 1 for patients' socio-demographic characteristics). When we posed the open probe, 26 unique references to uncertainty were made, whereas 66 unique references

were made after we posed the probes about the unpredictability of single events (aleatory uncertainty), and the imprecision of the risk estimates, their applicability to a specific patient (epistemic uncertainty). Fourteen of the 26 references to uncertainty following the open probe alluded to the unpredictability of single events, four alluded to the imprecision of the risk estimates, one alluded to the applicability of the probabilities to a specific patient, and seven were vague allusions to uncertainty or patients' struggle to cope with uncertainty.

Again patients seemed to have difficulty understanding what we were asking them when we probed specific elements of uncertainty. Patients mainly struggled with probes about the imprecision of the risk estimates and their applicability to a specific patient. Box 1 provides excerpts from an interview as an illustration of the struggle to formulate answers and inconsistencies between a patient's utterances. Of the six patients who indicated that there was no uncertainty with regard to the precision of prognostic estimates, four were highly numerate. Utterances about the imprecision of the risk estimates and their applicability to a specific patient frequently contained (logical) inconsistencies. An overview of inconsistent utterances within patients is provided in appendix Table 1 (enclosed in boxes).

Table 3 The frequency with which patients alluded to aleatory and epistemic uncertainty during the Standard Interview

	Open probe [a, b] N=62 allusions N (col%)	*Imprecision probe* [a, c] N=178 allusions N (col%)	*Example quotes*
Allusions to epistemic uncertainty			
Precision of the estimates			
Probabilities are exact/ no uncertainty about precision	0	20 (11)	"If they tell me it's 6%, then I think that's pretty definite. They wouldn't just say that." "Exact numbers, because his [oncologist] computer program is based on facts."
Probabilities are not fixed	1 (2)	38 (21)	"It's just statistics, not a fixed number." "The number doesn't really say much, it's just a probability of course. It gives an indication and not much more." "It [the survival probability] could definitely just as well be 16% or 18% …."
There is a margin around the probabilities	0	2 (1)	"I know there is a margin. They [the survival probabilities] are research figures."
Uncertainty associated with the model used to calculate probabilities	0	1 (<1)	"The program [Adjuvant! prediction model for breast cancer] is not precise."
Precision depends on sample size	0	2 (1)	"Depends on how many people took part. Difficult to estimate." "Statistics are not always reliable; you have to investigate a really large group… they're [the survival probabilities] just numbers. Not really exact."

[a]= Rows do not add up to the number of patients to whom we posed the probe, because some patients' answers contained multiple aspects. The percentages reflect how many patients said something about each specific element.
[b]= Open probe was: "*What do the probabilities [repeat probabilities the patient has already mentioned] mean to you?*"
[c]= Imprecision probe was: "*In your opinion, are the probabilities you were provided with during the consultation [repeat probabilities the patient has already mentioned] the exact survival probabilities… [pause] or could they be higher or lower for example?*"

Table 3 continued The frequency with which patients' alluded to aleatory and epistemic uncertainty during the Standard Interview (N (col%))			
	Open probe [a, b] **N=62 allusions** N (col%)	*Imprecision probe* [a, c] **N=178 allusions** N (col%)	*Example quotes*
Applicability of the estimates to individuals			
No uncertainty about the applicability to an individual	0	4 (2)	"Yes, very specifically with my characteristics and then a calculation was made on that [estimates by the Adjuvant! prediction model for breast cancer]."
The probabilities are averages	1 (2)	14 (8)	"I daren't say [whether the survival probabilities are precise]. Average numbers are different per person. That 20% [probability disclosed during the consultation] is an average I think, for one patient a little greater and for the other somewhat less."
Probabilities only apply at group level	8 (13)	30 (17)	"No, no, it doesn't mean anything… or no, it does mean something [the survival probabilities]. I think it's different for everybody. It just depends on whether it works or not." "It's [the survival probabilities] a theoretical given. Every person is different. It's [survival probabilities] a guideline."

[a]= Rows do not add up to the number of patients to whom we posed the probe, because some patient's answers contained multiple elements. The percentages reflect how many patients said something about each specific element.
[b]= Open probe was: "*What do the probabilities [repeat probabilities the patient has already mentioned] mean to you?*"
[c]= Imprecision probe was: "*In your opinion, are the probabilities you were provided with during the consultation [repeat probabilities the patient has already mentioned] the exact survival probabilities… [pause] or could they be higher or lower for example?*"

Table 3 continued The frequency with which patients' alluded to aleatory and epistemic uncertainty during the Standard Interview (N (col%))

	Open probe [a, b] N=62 allusions N (col%)	*Imprecision probe* [a, c] N=178 allusions N (col%)	*Example quotes*
Allusions to aleatory uncertainty			
Inability to predict single events	15 (24)	15 (8)	"It's just statistics, so you could also be one of the 7 in 100 that does get sick again." "If I don't do the endocrine therapy I have a greater chance that it [the cancer] will come back. But just the same, it might also never come back." "It could definitely just as well be 16% or 18% [the survival probabilities]. He can't categorically say that I am completely clean after the chemotherapy"
It's all or nothing	0	3 (2)	"I think I have two probabilities, either it comes back or it doesn't. The chance for either outcome is shown with percentages and those percentages are all averages, and not about me as an individual. They [the survival probabilities] might be true statistically, but as an individual you either get sick or you don't…"
There are no guarantees in life	22 (35)	22 (12)	"One could undergo everything [surgery and all adjuvant treatments] and it [the cancer] could still come back. They really stress that. There never are any guarantees…"
It's a lottery	0	1 (<1)	"…You never know, life's like a big slot machine… it remains a lottery."
General remarks on uncertainty	15 (24)	26 (15)	"*… It's just statistics*"

[a]= Rows do not add up to the number of patients to whom we posed the probe, because some patient's answers contained multiple elements. The percentages reflect how many patients said something about each specific element.
[b] = Open probe was: "*What do the probabilities [repeat probabilities the patient has already mentioned] mean to you?*"
[c] = Imprecision probe was: "*In your opinion, are the probabilities you were provided with during the consultation [repeat probabilities the patient has already mentioned] the exact survival probabilities… [pause] or could they be higher or lower for example?*"

Discussion

We investigated whether and which type of uncertainty oncologists disclose during consultations and explored patients' perceptions of the uncertainty associated with the probabilities discussed during their consultation. Additionally, we queried oncologists about their willingness to discuss uncertainty, and their practice in this regard. We found that communication of uncertainty is limited. First, oncologists talked about uncertainty in only half of the consultations. Second, if they did discuss uncertainty, oncologists infrequently discussed the imprecision of the risk estimates (epistemic or 2nd-order uncertainty), despite its potential relevance in the context of risk estimates produced by prediction models. Furthermore, the discussions that did occur most often consisted of vague allusions to imprecision. If oncologists referred to uncertainty, it was mostly (4 out of 5) an allusion to the unpredictability of single events (aleatory or 1st-order uncertainty).

The focus on disclosure of the unpredictability of single events may not be surprising as this type of uncertainty ('aleatory uncertainty') is relatively straightforward to discuss and comprehend. People are generally aware of the unpredictability of future events. Conversely, comprehending epistemic uncertainty (i.e. uncertainty about the precision of the risk estimates and their applicability to a specific patient) requires insight into the nature of probability and the origin of probability estimates. Clinicians may be hesitant to further complicate matters by bringing up a complex construct such as epistemic uncertainty bearing in mind that many people, even those highly educated, struggle to understand probabilistic information (1, 5). Moreover, the goal of discussing survival probabilities during consultations is to inform patients about their prognosis with and without adjuvant systemic treatment, and ultimately to help patients pass judgment about whether or not undergoing treatment is worthwhile (13). Clinicians may not want to undermine patients' confidence in probabilities by highlighting the limitations in their reliability or accuracy. Additionally, even if oncologists wish to discuss the imprecision of probabilities, this intent might be subverted by the fact that Adjuvant!, like other prediction models, does not provide such information. Perhaps due to the absence of information about precision, allusions to (im)precision were often somewhat vague.

Our study also shows that eliciting patients' perceptions of uncertainty is methodologically difficult. This may be due to the abstract nature of uncertainty. In addition, people may generally not give much thought to such uncertainty, possibly also for reasons of coping. As we interviewed patients shortly (within one week) after the consultation with their medical oncologist, it may have been difficult for them to delve too deeply into this topic. At the time of the consultation, they were still recuperating from surgery or undergoing radiotherapy. They may not have had the time to process all that happened to them recently and put it into perspective. Our questions may also have

caused anxiety by making patients aware of the fallibility of the probabilities guiding their treatment decisions. This posed a moral dilemma for the interviewers; they found themselves trying to find a balance between obtaining an answer to the research question and not distressing patients.

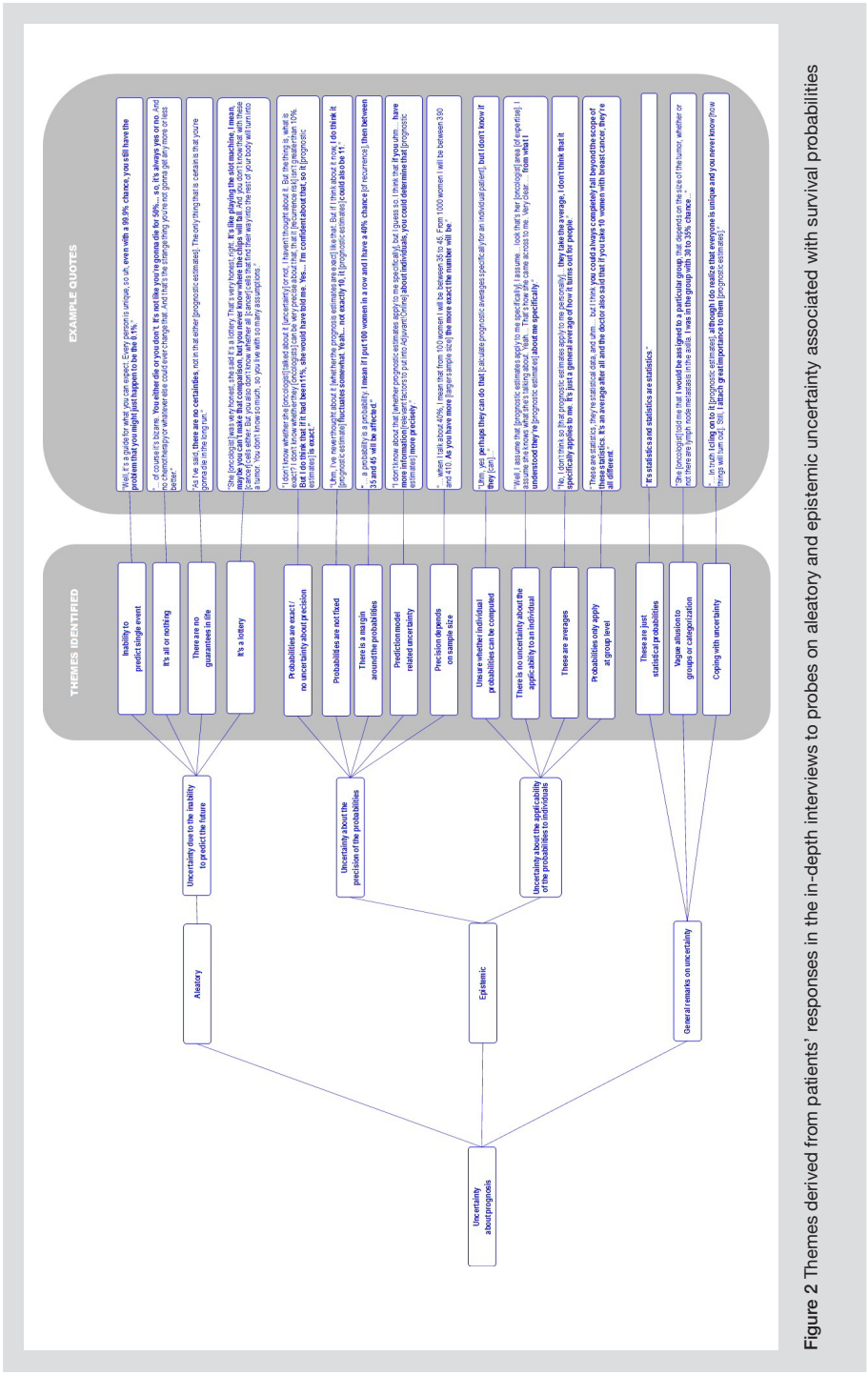

Figure 2 Themes derived from patients' responses in the in-depth interviews to probes on aleatory and epistemic uncertainty associated with survival probabilities

They dealt with this problem by dropping the probe if they perceived signs of apprehension in patients and then did not push the subject any further, even without having gotten a clear answer. This strategy limited the amount of information gained from the standard interviews and the potential inferences we can draw about patients' understanding of uncertainty. A deeper understanding requires probing much further in spite of patients' (perceived) apprehension. The face-to-face in-depth interviews were easier in this respect, but in those, we still ran into substantial incomprehension, perhaps mixed in with some apprehension and/or denial.

Patient A (61 years, highly numerate with stage II disease), her views on:

- **the certainty of the survival probabilities:**
"I cling to it [survival probability], whilst I secretly think, everyone is unique, so you never know. Yet, I still put a lot of… have a lot of faith in them [probabilities]"

- **the precision of the survival probabilities:**
"… uhm I've never thought about it [precision of probabilities]. But now I do think about it, I think it [the probability] does fluctuate a little. Yes, so not exactly 10, it could also be 11."

"… but I think it's more… what is precise? I don't know whether they [oncologists] can say it [survival probability] so precisely, that it's [survival probability] not greater than 10%. But I do think that if it had been 11% she would've told me. Yes… I'm confident about that, so it [survival probability] is exact."

"… on average it [survival probability] could also be higher. If you are in a group [with specific prognostic characteristics], you're in that group… and if you say that on average you have 10% chance of getting it [cancer] again… I'm not so good at this.... I don't think in terms of averages, because then it [10-year recurrence risk] could also be 5 or 15. I want to think about the 10% [recurrence risk after adjuvant treatment discussed during the consultation]."

- **whether her oncologist can predict her prognosis and to what extent available survival probabilities apply her personally:**
"I think so [it is possible to predict prognosis for an individual], but she [the oncologist] did not do it. She explained that I was in a certain group, but not everyone in that group is exactly the same… but an individual risk [estimate] might be possible. No no no, she based it [probabilities] on the group…"

"I do think she could have been more specific, but whether that would've been useful, a single percent [higher or lower on an individual level]. If you got your own percentage [survival probability] it could deviate from 10… a little bit. It wouldn't be far off."

Box 1 Example of answers during an in-depth interview

Patients seemed to struggle with information about uncertainty. This was most true for the imprecision in probability estimates (epistemic uncertainty), and least with the fundamental inability to predict individual futures (aleatory uncertainty). We observed many logical contradictions in patients' answers. In addition, if not specifically asked

about uncertainty, only about one in four referred to uncertainty, and three out of five of those utterances were allusions to the unpredictability of single events. Even when we specifically asked about the imprecision of risk estimates and their applicability to a specific patient, almost one in four utterances were allusions to the unpredictability of single events. It is unclear whether patients do not perceive epistemic uncertainty, or whether they did not understand what we were asking them. For example, when asked about imprecision, patients seemed to think that we were asking whether the probabilities were true – i.e., whether their oncologist had got them right or whether he/she had been truthful with them. They seemed unable to reconcile the thought that a probability can be correct and at the same time not be exact. These seemingly incompatible realities may account for some of the inconsistencies in patients' perceptions of uncertainty. Previous reviews have also identified a struggle to reconcile seemingly incompatible realities; in those cases, patients tried to reconcile the need to be fully informed about prognosis with not being overwhelmed with complex medical information (17, 18). Patients seem to use 'positive thinking', or even an element of denial in their recall of prognostic information (19, 20). Perhaps such coping strategies also play a role here, which may at least partly explain the logical inconsistencies we observed.

Most patients seem to realize that the unpredictability of single events is inherent to probabilities, but across education and numeracy levels they do place value on probability information. These probabilities seem to satisfy patients' need to have some sense of certainty to cling to (e.g., "*I attach a lot of value [to the probabilities] ... in truth, I cling to them [probabilities], even though I think to myself, everyone is unique…*"). Patients seem to perceive the unpredictability of single events as an inevitable part of life (e.g., "*…there are no guarantees in life, not with this [cancer]… not with anything.*"), but uncertainty about the precision of the risk estimates and their applicability may be more challenging to cope with. Acknowledging this type of uncertainty may undermine the sense of security some patients seem to derive from the probabilities communicated during the consultation (e.g., "*I don't think in terms of averages, because then it [10-year recurrence risk] could also be 5 or 15. I want to think about the 10% recurrence risk after adjuvant treatment discussed during the consultation*"). Conversely, it has been suggested that if explicit prognostic information, including its associated uncertainty, is coupled with appropriate emotional support it could be a way of decreasing anxiety, generating greater self-efficacy and ultimately achieving a better quality of life (21). Research is needed to investigate whether this approach is effective in the curative setting.

This is the first study to investigate disclosure of uncertainty during real-time consultations, and to explore perceptions of uncertainty in a large sample of patients. Currently, it is increasingly common for clinicians to discuss probabilities during consultations with patients. Whether disclosure of uncertainty should be part of risk communication or

not, however, is a matter of debate. This debate has so far been based on ethical and/or practical concerns. The available evidence is limited and most work in this area has been experimental or focused on healthy subjects' perceptions of uncertainty (e.g., (2)). Therefore, although informative, the currently available evidence might not be the best indication of how actual patients, especially those facing a potentially life-threatening illness, perceive and understand information about uncertainty.

We did not assess whether uncertainty was communicated during consultations in which prognostic estimates were not communicated. The current debate revolves around whether the uncertainty surrounding risk estimates (e.g., survival estimates) should be communicated whenever these risk estimates are communicated to patients. Therefore, we opted to focus on consultations in which prognostic estimates had been discussed. Further, in the consultations in which no prognostic estimates were discussed, oncologists can only have discussed aleatory uncertainty.

Our study showed that there is wide variability in the communication of uncertainty, and that clarity is often lacking. Oncologists infrequently fully inform their patients about uncertainty around the probabilities given. This is especially true for the uncertainty concerning precision and applicability to individuals. When communicated, such information turns out to be difficult to understand. If clinicians wish patients to become aware of this type of uncertainty, its inherent complexity makes it imperative that such information be presented in a clear manner. Otherwise, the meaning behind clinicians' statements is likely to be lost on most patients. Witteman *et al.* developed pictographs with animated random dispersal of risk events, and the effect of such pictographs has been evaluated in healthy subjects (22, 23). Such visual display formats could facilitate communication about uncertainty, and increase patient awareness of the random nature of probabilities. However, no clear guidance exists today on how best to inform patients about uncertainty, more research is needed. In the meantime, it is clear that it is important to raise awareness in communication skills training about the importance of clearly formulating information about uncertainty if oncologists choose to discuss it with patients. For now it seems that patients can grasp aleatory uncertainty, but have difficulty with epistemic uncertainty.

It was not our aim to assess whether or not there is a discrepancy between oncologists' perception about the frequency with which they disclose uncertainty and their actual disclosure. To answer this question, oncologists should be asked after each consultation whether or not they communicated uncertainty. Such a question could have predisposed oncologists to discuss uncertainty more often than they normally would have, hindering our aim, i.e., to observe what currently happened in clinical practice. It may be of value for future research to explore whether or not oncologists' perception about how often they disclose uncertainty is congruent with observed disclosure during consultations.

Oncologists might feel they communicated uncertainty, but for example the way they formulate this information is not clear or explicit enough. Indeed in the current study we found that especially communication about epistemic uncertainty was somewhat vague. Results of such studies may help shape communication training.

Interestingly, the moral dilemma we encountered while probing patients during the interviews is comparable to the difficulty oncologists face, trying to balance complete information provision and not causing unnecessary confusion and/or distress in patients, and not overwhelming them with too much information. If the problems we encountered during the interviews mainly arise from a lack of understanding, the focus of future research should be on how clinicians can best inform their patients about uncertainty. Alternatively, perhaps the most urgent question currently is whether uncertainty should be communicated at all. If indeed not paying attention to uncertainty may help patients to better cope with their disease, the imperative of autonomy and full disclosure may contradict that of well-being (24, 25). Our findings suggest that the question how to communicate the uncertainty of risk estimates may be secondary to the question whether patients benefit from such information. This dilemma deserves careful consideration in future research.

References

1. Gigerenzer G, Gaissmaier W, Kurz-Milcke E, et al.: Helping Doctors and Patients Make Sense of Health Statistics. Psychol Sci Publ Interest 8:53-96, 2007
2. Han P, Lehman T, Massett H, et al.: Conceptual problems in laypersons' understanding of individualized cancer risk: a qualitative study. Health Expect 12:4-17, 2009
3. Politi M, Han P, Col N: Communicating the Uncertainty of Harms and Benefits of Medical Interventions. Medical Decision Making 27:681-695, 2007
4. Han PK: Conceptual, methodological, and ethical problems in communicating uncertainty in clinical evidence. Med Care Res Rev 70:14S-36S, 2013
5. Lipkus I, Samsa G, Rimer B: General performance on a numeracy scale among highly educated samples. Med Decis Making 21:37-44, 2001
6. Burstein H, Temin S, Anderson H, et al.: Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol 32:2255-2269, 2014
7. Early Breast Cancer Trialists' Collaborative Group: Tamoxifen for early breast cancer: an overview of the randomised trials. The Lancet 351:1451-1467, 1998
8. Early Breast Cancer Trialists' Collaborative Group: Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100_000 women in 123 randomised trials. The Lancet 379:432-444, 2012
9. Early Breast Cancer Trialists Collaborative Group: Polychemotherapy for early breast cancer: an overview of the randomised trials. The Lancet 352:930-942, 1998
10. NABON: Breast cancer, Dutch Guideline, version 2.0, in . The Netherlands, 2012
11. Adjuvant! Inc.: Adjuvant! for Breast Cancer (Version 8.0), in , 2011
12. Agarwal V, O'Neill P: Adjuvant! Online as a Decision-making Tool in Early Breast Cancer: a UK National Survey. Clin Oncol (R Coll Radiol) 23:159-160, 2011
13. Engelhardt EG, Pieterse AH, van Duijn-Bakker N, et al.: Breast cancer specialists' views on and use of risk prediction models in clinical practice: A mixed methods approach. Acta Oncol:1-7, 2014
14. National Comprehensive Cancer Network (NCCN): Clinical Practice Guidelines in Oncology: Breast Cancer version 1.2014, in , 2013
15. NICE: Early and locally advanced breast cancer: diagnosis and treatment, in , 2009
16. Gerrity M, White K, DeVellis R, et al.: Physicians' Reactions to Uncertainty: Refining the constructs and scales. Motiv Emot 19:175-191, 1995
17. Hagerty R, Butow P, Ellis P, et al.: Communicating prognosis in cancer care: a systematic review of the literature. Ann Oncol 16:1005-1053, 2005
18. Johnson M, Tod A, Brummell S, et al.: Prognostic communication in cancer: A critical interpretive synthesis of the literature. Eur J Oncol Nurs 19:554-567, 2015
19. Mendick N, Young B, Holcombe C, et al.: Telling "everything" but not "too much": the surgeon's dilemma in consultations about breast cancer. World J Surg 35:2187-2195, 2011
20. Jansen J, Butow P, van Weert J, et al.: Does age really matter? Recall of information presented to newly referred patients with cancer. J Clin Oncol 26:5450-5457, 2008

21. van Vliet L, van der Wall E, Plum N, et al.: Explicit prognostic information and reassurance about nonabandonment when entering palliative breast cancer care: findings from a scripted video-vignette study. J Clin Oncol 31:3242-3249, 2013

22. Witteman HO, Fuhrel-Forbis A, Wijeysundera HC, et al.: Animated randomness, avatars, movement, and personalization in risk graphics. J Med Internet Res 16:e80, 2014

23. Han PK, Klein WM, Killam B, et al.: Representing randomness in the communication of individualized cancer risk estimates: effects on cancer risk perceptions, worry, and subjective uncertainty about risk. Patient Educ Couns 86:106-113, 2012

24. Beauchamp T, Childress J: Principles of Biomedical Ethics (ed 7). New York, Oxford University Press, 2013

25. Vos M, Putter H, van Houwelingen H, et al.: Denial and social and emotional outcomes in lung cancer patients: The protective effect of denial. Lung Cancer 72:119-124, 2011

Appendix A Interview protocol to explore patient awareness and perceptions about uncertainty

1. Open probe assessing patients' awareness of the uncertain nature of the prognostics estimates discussed if this is not brought up by the interviewer (= *open probe without priming*):
Open probe assessing patients' awareness of uncertainty associated with the survival estimates, without introducing the concept of uncertainty: What did you think about when you first heard these probabilities?

Then the interviewer explicitly stated that some of the questions that would next be posed might be a bit abstract and difficult. We made clear that we were in no way implying that she did not understand the information correctly or that her oncologist withheld information or provided her with incorrect information. We explained that we only wanted to know if she has ever thought about the following concepts and what her views are.

2. Probes for specific elements of uncertainty:

a. Open probe assessing patients' views on the certainty of the survival estimates, after introducing the concept of uncertainty (= certainty probe): We have just talked about the probabilities from ...[name source].. you had talked about with dr…. In your opinion, how certain are the risk estimates your doctor gave you? How much confidence or faith do you have in those probabilities?

b. Probe assessing patients' views on the precision of the risk estimates (= precision probe): How precise or exact do your risk estimates seem? [pause, allowing the patient room to respond] For example, do you think it's possible that your actual risk is higher or lower?

c. Probe assessing patients' views on their oncologist's ability to predict single events (= predicting future/applicability to individual probe):
- In your opinion, to what extent do you think your oncologist is able to predict your prognosis, for you as an individual?
- To what extent do you feel the risk estimates you discussed with your oncologist apply to you personally?

3. Probe to assess whether patients felt they had been informed about uncertainty:

a. We have talked at length about your views on how exact the probabilities you discussed with dr. … are and whether you think they apply to you personally. We were

keen to find out whether you had ever given it any thought and what your thoughts are on this subject. We would also like to know, did you discuss any of these issues with your oncologist?
b. If patient answers *yes*:
What did dr. … say about this?

Appendix Table 1 Overview of patients' characteristics, probes posed and themes discussed in the In-depth interviews																
Participant ID	**P11**	**P12**	**P13**	**P14**	**P15**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P31**	**P32**	**N**
Overview of probes that the interviewer posed[a]																
Open probes																
Without priming	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	15
With priming				x			x	x	x	x		x	x	x	x	9
Epistemic uncertainty																
Precision of the estimates	x	x			x		x	x	x	x		x	x	x	x	11
Applicability to individual probe	x			x			x	x	x		x	x	x	x	x	10
Aleatory uncertainty																
Predicting future events probe	x			x			x	x	x		x	x	x	x	x	10
Patient perception whether oncologist discussed uncertainty	x				x			x	x				x	x	x	7
Patient utterances about uncertainty made after the interviewer posed the *Open Probe*																
No utterances about uncertainty					x			x				x				3
Allusions to aleatory uncertainty																
Inability to predict single events	x			x			x		x		x			x		6
It's all or nothing		x												x		2
There are no guarantees in life			x				x			x				x	x	5

Abbreviations: N= number; X= yes
a= see Appendix 2 for the interview protocol

Appendix Table 1 continued Overview of patients' characteristics, probes posed and themes discussed in the In-depth interviews																
Participant ID	**P11**	**P12**	**P13**	**P14**	**P15**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P31**	**P32**	**N**
Patient utterances about uncertainty made after the interviewer posed the *Open Probe*																
It's a lottery				x												1
Allusions to epistemic uncertainty																
A. Precision of the estimates																
Estimates are exact – no uncertainty about precision						x										1
Estimates are not fixed																0
There is a margin around the estimates		x													x	2
Uncertainty associated with the model used to calculate probabilities																0
Precision depends on sample size															x	1
B. Applicability of the estimates to individuals																
Unsure whether individual probabilities can be computed																0
No uncertainty about the applicability to an individual																0
The probabilities are averages																0
Probabilities only apply at group level															x	1
Abbreviations: N= number; X= yes a= see Appendix 2 for the interview protocol																

Appendix Table 1 continued Overview of patients' characteristics, probes posed and themes discussed in the in-depth interviews																
Participant ID	**P11**	**P12**	**P13**	**P14**	**P15**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P31**	**P32**	**N**
Patients' utterances about uncertainty made after the interviewer posed the *Open Probe*																
General remarks about uncertainty																
These are just statistical probabilities	x	x							x				x			4
Vague allusion to group size or categorization													x			1
Coping with uncertainty				x										x		2
Patients' utterances about uncertainty made after the interviewer posed probes for specific elements of uncertainty																
Allusions to aleatory uncertainty																
Inability to predict single events	x	x		x			x	x	x				x		x	8
It's all or nothing		x														1
There are no guarantees in life				x			x	x		x			x			5
It's a lottery	x			x												2
Allusions to epistemic uncertainty																
A. Precision of the estimates																
Probabilities are exact - no uncertainty about precision							x	x	x			x	x	x		6
Estimates are not fixed	x	x						x					x		x	5
There is a margin around the estimates	x								x				x			4
Abbreviations: N= number; X= yes a= see Appendix 2 for the interview protocol																

Appendix Table 1 continued Overview of patients' characteristics, probes posed and themes discussed in the in-depth interviews																
Participant ID	**P11**	**P12**	**P13**	**P14**	**P15**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P31**	**P32**	**N**
Uncertainty associated with the model used				x										x		2
Precision depends on sample size															x	1
B. Applicability of the estimates to individuals																
Unsure whether individual probabilities can be computed				x												1
No uncertainty about the applicability to an individual				x			x		x			x	x	x		6
The estimates are averages	x			x					x		x	x	x			6
Estimates only apply at group level	x			x	x			x	x	x	x		x		x	9
Patients' utterances about uncertainty made after the interviewer posed probes for specific elements of uncertainty																
General remarks about uncertainty																
These are just statistical estimates	x		x	x			x	x	x							6
Vague allusion to group size or categorization	x						x	x								3
Coping with uncertainty			x													1
Patient indicated that uncertainty had been discussed by oncologist		x														1

Abbreviations: N= number; X= yes
a= see Appendix 2 for the interview protocol