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Towards personalized treatment for high risk endometrial cancer

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Chapter 3

Patients' and clinicians' preferences in adjuvant treatment for high risk endometrial cancer: implications for shared decision making

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ABSTRACT

Background

Decision making regarding adjuvant therapy for high risk endometrial cancer is complex. The aim of this study was to determine patients' and clinicians' minimally desired survival benefit to choose chemoradiotherapy over radiotherapy alone. Moreover, influencing factors and importance of positive and negative treatment effects (i.e. attribute) were investigated.

Methods

Patients with high risk endometrial cancer treated with adjuvant pelvic radiotherapy with or without chemotherapy and multidisciplinary gynecologic oncology clinicians completed a trade-off questionnaire based on PORTEC-3 trial data.

Results

In total, 171 patients and 63 clinicians completed the questionnaire. Median minimally desired benefit to make chemoradiotherapy worthwhile was significantly higher for patients versus clinicians (10% vs 5%; $p = .02$). Both patients and clinicians rated survival benefit most important during decision making, followed by long-term symptoms. Older patients (OR 0.92, 95% CI 0.87–0.97; $p = .003$) with comorbidity (OR 0.34, 95% CI 0.12–0.89; $p = .035$) had lower preference for chemoradiotherapy, while patients with better numeracy skills (OR 1.2, 95% CI 1.05–1.36; $p = .011$) and chemoradiotherapy history (OR 25.0, 95% CI 8.8–91.7; $p < 0.001$) had higher preference for chemoradiotherapy.

Conclusions

There is a considerable difference in minimally desired survival benefit of chemoradiotherapy in high risk endometrial cancer among and between patients and clinicians. Overall, endometrial cancer patients needed higher benefits than clinicians before preferring chemoradiotherapy.

Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries. Although most women with endometrial cancer are diagnosed at early stage of disease, 15–20% are diagnosed with high risk disease with increased incidence of recurrence and cancer-related death. The PORTEC-3 trial investigated the treatment effect of combined adjuvant pelvic radiotherapy and chemotherapy versus pelvic radiotherapy alone for women with high risk endometrial cancer. The updated survival analysis showed a 5-year overall survival (OS) benefit of 5% (81% vs 76%, HR 0.70, $p = 0.034$) and failure-free survival benefit of 7% (76% vs 69%, HR 0.70, $p = 0.016$) with chemoradiotherapy as compared to radiotherapy alone, with the greatest benefit of 10% or more observed in women with serous cancers and those with stage III disease.[1] Toxicity is most frequent and severe during treatment, but the lower grade toxicities, which may have long-term impact, should not be neglected. Pelvic radiotherapy is associated with higher risks of long-term gastrointestinal and genitourinary symptoms, with impact on physical and role functioning.[2, 3] Adding chemotherapy leads to additional symptoms that may persist (e.g. persisting tingling or numbness of hands or feet reported by 25% of the patients at 3 and 5 years after treatment, and a small deterioration in physical and role functioning during the first 3 years after treatment).[4] Weighing these pros and cons reflects the complexity of shared decision-making on adjuvant treatment for patients with high risk endometrial cancer.

The current analysis was initiated to investigate preferences of women with high risk endometrial cancer and multidisciplinary clinicians. The actual differences in survival and symptoms were presented, in order to determine which benefit exceeded the risks sufficiently to consider the addition of chemotherapy to radiotherapy worthwhile in women with high risk endometrial cancer. In addition, factors influencing the decision and the importance assigned to the major positive and negative treatment outcomes were investigated.

Participants and methods

Study population and procedures

For the patient study, patients with high risk endometrial cancer were enrolled in 12 radiation oncology centers across the Netherlands. Selection criteria were: surgery with curative intent with adjuvant pelvic radiotherapy with or without chemotherapy; treated after 2014; alive without recurrent disease reported until last follow-up; no other cancer; able to read Dutch. Because of the pragmatic nature of the study and the fact that the indication of adjuvant pelvic radiotherapy is limited to endometrial cancer with high risk

features we used diagnosis and treatment codes for selecting patients from the hospital databases. Patients were approached via their treating radiation oncologist by letter. Patients were asked to fill out a self-administered web-based questionnaire. On request, a paper version was available. An anonymized approach without linked patient report data was used, therefore no reminders could be sent. We pilot-tested the questionnaire in a sample with varied medical history across the Netherlands.

For the clinician study, we approached multidisciplinary gynecologic oncology clinicians (including radiation oncologists, gynecologic oncologists and medical oncologists) via the Dutch Gynecologic Oncology Group. Clinicians were approached via email with a link to the web-based questionnaire. After two weeks clinicians received a reminder. Question validation was enabled in the web-based questionnaire to prevent missing values. The Medical Ethics Committee of Leiden University Medical Centre approved the study.

Measures

For the patient study, clinical factors (cancer treatment history and any comorbidities influencing daily life) and sociodemographic factors, health literacy[5] and numeracy[6], treatment preferences and attribute importance ratings were assessed (Appendix A1 displays the health literacy and numeracy questions). For the clinician study, sociodemographic factors, affiliation and main specialty, treatment preferences and attribute importance ratings were assessed.

Participants' minimally desired 5-year overall survival benefit (MDSB) from chemoradiotherapy as compared to radiotherapy alone was assessed using the treatment trade-off method.[7] Patients and clinicians were asked to imagine that they had recently been diagnosed with high risk endometrial cancer and that their clinician offered them two treatment strategies. We made explicit that the situation was hypothetical and did not refer to their individual situation. Based on known data from the quality of life analysis of the PORTEC-3 trial, an overview with the most frequent symptoms and deterioration in functioning was presented (available in Appendix A2). The importance assigned to every treatment outcome (attribute) was rated using a 4-point Likert-type response scale. Subsequently, participants were asked what treatment option they preferred at a 5% benefit of additional chemotherapy. If they chose radiotherapy alone, the survival benefit with addition of chemotherapy varied with 5% increments to a maximum benefit of 25% over the baseline of 75% until they switched their preference. When participants had chosen chemoradiotherapy at 5% or 10% survival benefit, they were asked for their MDSB (multiple choice question ranging between 1 and 5% or 6 and 10%, respectively).

Statistical analysis

Empty returned questionnaires, those with information on characteristics only, and those with inconsistent answers among the trade-off questions were excluded for analysis as displayed in Figure 1. The analysis was primarily descriptive. Categorical variables were compared using Fisher's exact test or chi-square test. Continuous and ordinal variables were compared using Mann-Whitney *U* test or Kruskal-Wallis test. The following groups were compared: (A) patients versus clinicians, (B) patients previously treated with adjuvant radiotherapy alone versus chemoradiotherapy, (C) the three clinician specialties.

Univariable and multivariable logistic regression with likelihood-based backward selection were performed to identify predictors for chemoradiotherapy preference at a 5% survival benefit.

A two-sided *p*-value ≤0.05 was considered statistically significant for the treatment trade-off and logistic regression. For comparison of attribute importance ratings, a two-sided *p*-value ≤0.01 was considered statistically significant and ≤0.05 was considered a trend to guard against false-positive results due to multiple testing. Statistical analyses were done with R version 3.6.1.

Results

In total, 453 eligible patients were approached. Of these patients, 205 (45%) started the questionnaire, of which 171 (83%) were evaluable (131 online (77%) and 40 paper (23%); Fig. 1). Among the 106 clinicians approached, 63 (59%; 21/39 radiation oncologists, 34/54 gynecologic oncologists, and 8/13 medical oncologists) completed the online questionnaire. Table 1 shows the baseline characteristics for both patients and clinicians.

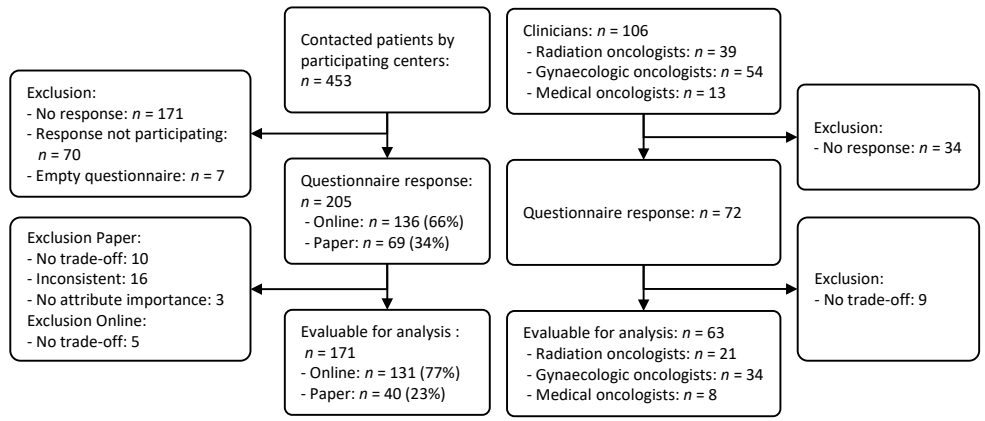

Figure 1. Flowchart

Median Subjective Numeracy Scale score was 14 (IQR 11–16) on a scale from 3 to 18 with larger scores indicating a higher subjective rating of numeracy. Median literacy score was 6 (IQR 5–7) on a scale from 0 to 12 with higher scores reflecting greater problems with reading.

Treatment preference and minimally desired survival benefit

At a 5% survival benefit, 69 (40%) of the patients and 41 (65%) of the clinicians preferred chemoradiotherapy over radiotherapy alone ($p = 0.001$). In Table 2 the MDSB ratings are listed. Figure 2 shows the cumulative proportion of participants preferring chemoradiotherapy according to MDSB. Overall, the median MDSB for preferring chemoradiotherapy was significantly higher for patients than for clinicians (10% vs 5%, $p = 0.024$). Patients who had received chemoradiotherapy had a significantly lower MDSB than patients who had received radiotherapy alone (2% vs 10%, $p < 0.001$). There was no significant difference between the clinician specialties ($p = 0.46$).

Table 1. Participant characteristics

Patients	***n* = 171**
Age, years (median [IQR])	67 [60-72]
Marital status (%)	
Married/Living together	100 (58.5)
Partner, living alone	6 (3.5)
No partner/widow	65 (38.0)
Having children = Yes (%)	121 (70.8)
Educational level (%)	
Low	69 (40.4)
Intermediate	49 (28.7)
High	50 (29.2)
Other	3 (1.8)
Main daily activity (%)	
Paid/unpaid job	54 (31.6)
Leisure and IADLS	117 (68.4)
Comorbidity = Yes (%)	123 (71.9)
Received radiotherapy (%)	
EBRT	95 (56.2)
EBRT+VBT	69 (40.8)
VBT	5 (3.0)
Chemotherapy = Yes (%)	42 (24.6)
Time since diagnosis in, years (median [IQR])	3 [2-5]

Clinicians	***n* = 63**
Age, years (median [IQR])	50 [43-56]
Sex (%)	
Male	16 (25.4)
Female	47 (74.6)
Specialty (%)	
Radiation oncology	21 (33.3)
Gynecologic oncology	34 (54.0)
Medical oncology	8 (12.7)
Current institution (%)	
General	28 (44.4)
Academic	25 (39.7)
Categorical	10 (15.9)
Number of EC patients per month (median [IQR])	4 [2-5]

Education level: low = elementary school, completed lower general secondary education/vocational training; intermediate: higher secondary educational/vocational training; high = higher professional education, university, doctor; EBRT = external beam radiotherapy; EC = endometrial cancer; IADLS: instrumental activities of daily living; VBT = vaginal brachytherapy.

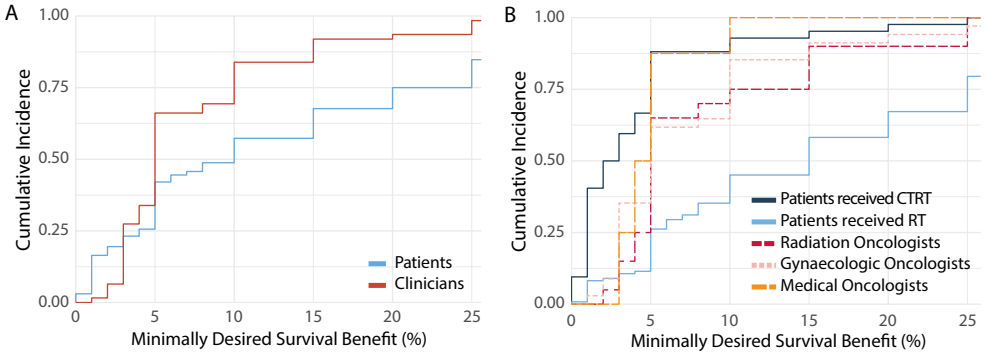

Figure 2. Cumulative proportion of participants preferring chemoradiotherapy over radiotherapy alone according to minimally desired survival benefit by patients versus clinicians (A) and their subgroups (B). Baseline 5-year survival rate with radiotherapy alone is 75%. The maximum survival benefit is 25% corresponding to a 5-year survival rate of 100%. Numbers do not add up to 1.00 because of those declining chemoradiotherapy irrespective of any survival benefit. CTRT = chemoradiotherapy; RT = radiotherapy.

Table 2. Minimally desired survival benefit (MDSB) from chemoradiotherapy

		Percentile					
	MDSB	**25th**	**75th**	**5th**	**95th**	**NA**	***p*-value**
							0.024*
Patients (*n*=171)	10	4	20	1	infin.	7	<0.001†
Received Pelvic Radiotherapy (n=129)	15	5	25	1	infin.	7	
Received Chemoradiotherapy (n=42)	2	1	5	0	15		
Clinicians (*n*=63)	5	3	10	2	25	1	0.46†
Radiation oncologists (n=21)	5	4	10	2	25	1	
Gynecologic oncologists (n=34)	5	3	10	2	20		
Medical oncologists (n=8)	4	3	5	3	10		

p values less than or equal to 0.05 were deemed significant

*Between group comparison: patients versus clinicians; †Within group comparison

Attribute importance

Figure 3 shows the distribution of importance assigned to each attribute by patients and clinicians. Survival benefit was judged as the most important attribute, followed by the long-term symptoms (i.e. '25% with persistent tingling/numbness', and 'small decline in physical functioning'), both by patients and clinicians. There was a trend for patients judging moderate deterioration in physical functioning during treatment more important ($p = 0.025$) and persistent tingling/numbness less important ($p = 0.027$) than clinicians. The treatment duration was judged as least important, especially by clinicians (judged as not important by 30% of patients vs 43% of clinicians, $p < 0.001$). Patients considered diarrhea ('36% during treatment for both treatment groups'; $p = 0.001$) and social functioning during treatment ('moderate deterioration'; $p = 0.003$) more important in their decision than clinicians.

Patients who had received chemoradiotherapy judged treatment duration less important than those who had received radiotherapy alone (judged as not important by 55% [CTRT] vs 22% [RT], $p < 0.001$), as well as hair loss during treatment (36% vs 16%, $p = 0.003$). In addition, there was a trend for several other negative attributes to be judged less important by patients who had received chemoradiotherapy (Appendix Figure B1). There were no statistically significant differences in attribute importance between the three clinician specialties. However, there was a trend for different ratings of short-term fatigue and quality of life, and short- and long-term functioning importance, with radiation oncologists rating these attributes of higher importance than other specialists ($p < 0.05$; Appendix Figure B2).

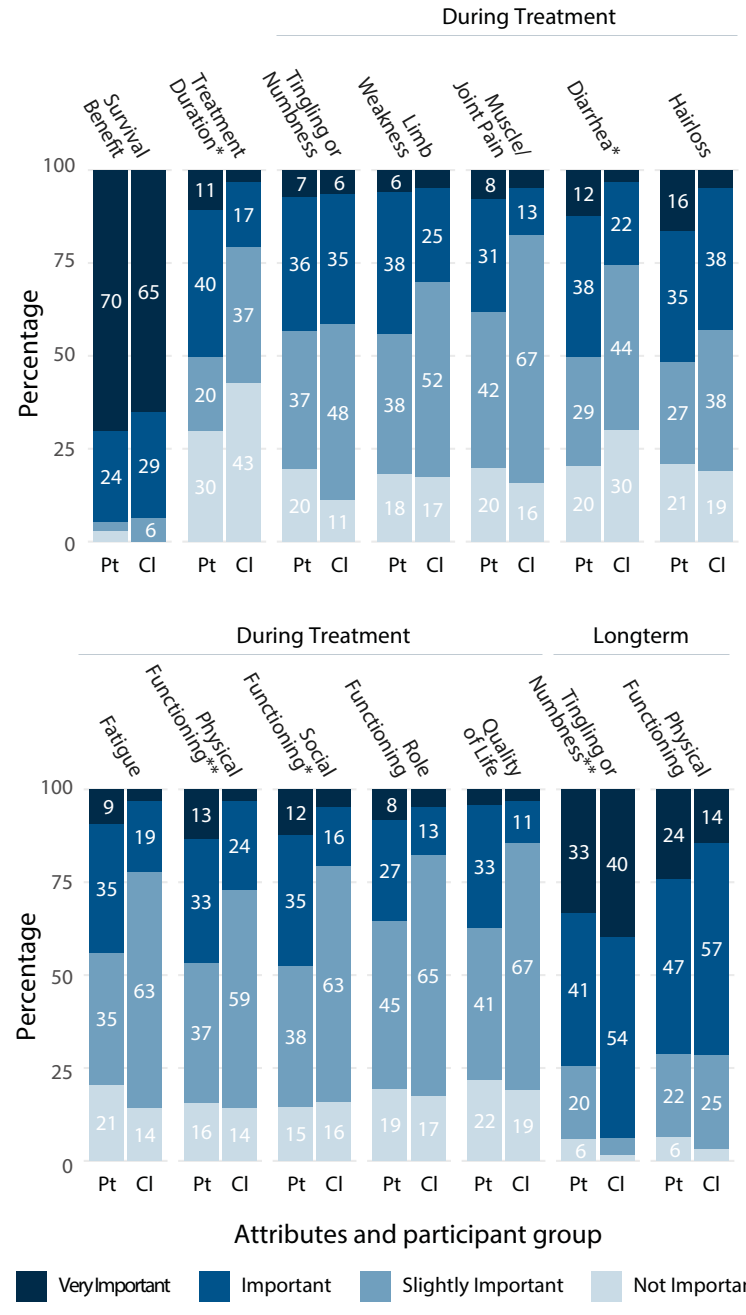

Figure 3. Attribute importance ratings in decision making

Attribute importance ratings in the decision between chemoradiotherapy and radiotherapy alone after reading the trade-off overview with a 5% survival benefit. Pt = patients; Cl = clinicians.

*p value less than or equal to 0.01 shows significance; **p value less than or equal to 0.05 shows a trend.

Factors influencing treatment preference

Multivariable logistic regression showed that patients with an older age (OR 0.92, 95% CI 0.87–0.97; $p = 0.003$) and comorbidity (OR 0.34, 95% CI 0.12–0.89; $p = 0.035$) were less likely to prefer chemoradiotherapy, while those with a higher subjective numeracy score (OR 1.2, 95% CI 1.05–1.36; $p = 0.011$) and a chemoradiotherapy history (OR 25.0, 95% CI 8.8–91.7; $p < 0.001$) were more likely to prefer chemoradiotherapy over radiotherapy alone (Table 3). For clinicians, none of baseline variables entered in the multivariable logistic regression model were statistically significant predictors (data not shown).

Table 3. Predictors of preference for chemoradiotherapy at a 5% survival benefit among patients

	Univariable logistic regression				Multivariable logistic regression			
	OR	**Lower 95% CI**	**Upper 95% CI**	***p***	**OR**	**Lower 95% CI**	**Upper 95% CI**	***p***
Age	0.92	0.88	0.96	<0.001	0.92	0.87	0.97	0.003
Comorbidity (Yes vs No)	0.35	0.15	0.73	0.007	0.34	0.12	0.89	0.035
Received CTRT (Yes vs No)	26.3	9.59	93.1	<0.001	27.5	9.22	106	<0.001
Subjective Numeracy Scale	1.13	1.03	1.24	0.015	1.18	1.05	1.36	0.011

p values less than or equal to 0.05 were deemed significant

CTRT = chemoradiotherapy; IADLS = instrumental activities of daily living; OR = odds ratio for chemoradiotherapy preference in the decision between chemoradiotherapy and radiotherapy alone after seeing the trade-off overview with a 5% survival benefit; 95% CI = 95% confidence interval.

Discussion

This patient preference study for high risk endometrial cancer showed that patients desired higher survival benefits than clinicians before preferring adjuvant chemoradiotherapy over radiotherapy alone. The minimally desired survival benefit varied considerably among both patients and clinicians. Patients' preferences were strongly influenced by treatment history. In addition, younger age, having no comorbidities and higher subjective rating of numeracy were predictors of the preference for chemoradiotherapy. Survival benefit was judged to be the most important attribute in decision making by both patients and clinicians, followed by the risk of developing long-term symptoms (i.e. neuropathy and impaired physical functioning).

Patients had a median MDSB of 10% over the baseline 5-year survival rate of 75% with radiotherapy alone, while clinicians had a median MDSB of 5% to make adjuvant chemoradiotherapy worthwhile. It was unexpected that we found different results compared to those of the previous patient preference study related to the PORTEC-3 trial. The ANZGOG sub-study among 83 high risk endometrial cancer patients recruited to the PORTEC-3 trial found that patients, compared to clinicians, desired lower benefits to make

chemoradiotherapy worthwhile (4% vs 10% over a 5-year survival rate of 65%).[8] Having encountered the symptoms and adverse events of patients, but particularly knowing the results of the PORTEC-3 trial (5% benefit) may have made the clinicians in our study less reluctant in accepting chemotherapy for a small benefit. The relatively low survival benefit desired among patients in the ANZGOG sub-study may be explained by the selection of patients who had decided to take part in the PORTEC-3 trial and thus were likely to accept chemotherapy for an uncertain benefit. Meanwhile, patient preferences in our study were influenced by treatment history, and most patients (75%) did not receive chemotherapy.

The variability of MDSB was high, although the range among clinicians was slightly narrower than among patients. This high variability in preferences has been reported by others as well.[8-10] Younger age, having no comorbidity and better numeracy skills were predictive for preferring chemoradiotherapy in our study, while most studies report a lack of predictors. Nevertheless, individual treatment preferences remain hard to predict from baseline characteristics, and are most likely influenced by a complex of experiences, values and attitudes. Treatment preferences are clearly influenced by actual treatment received. Many studies have reported that patients who are about to undergo treatment or have experienced a treatment generally adapt to their decision by having stronger preference for that treatment.[9, 11, 12] This is a known psychologic process to make preferences agree with the preceding decision called cognitive dissonance reduction or cognitive justification. In the shared decision making process, it may be helpful to explore the patient's prior experience with the treatments considered, e.g. in close family members, and discuss the potential bias this may have caused.

We did not find a significant difference in MDSB between clinicians from different specialties. Previous research reported that clinicians generally need less benefit from the treatment of their own specialty.[9, 13, 14] The fact that this was not found in our study may be explained by the small number of medical oncologist, multidisciplinary treatment approach in current practice and knowledge of the PORTEC-3 trial results.

The most important attribute in decision making, for both patients and clinicians, was survival benefit. This has been reported in several cancer preference studies.[15, 16] However, thorough evaluation of multiple attributes, especially with distinction of short-term and long-term impairments, is novel. Some studies emphasized the importance of quality of life in general, but without detailed attributes.[16, 17] We found that the risk of developing long-term symptoms (i.e. neuropathy and impaired physical functioning) is of high importance to patients. While treatment duration was considered the least important attribute, all short-term symptoms and impairments were of intermediate importance.

There were clear strengths to our study. First, many patients across our entire country participated to represent the Dutch high risk endometrial cancer population. This, together with the relative large sample size allowed subgroup analysis and multivariable logistic regression. Second, the presented information on survival and long-term symptoms were based on the actual data of the randomized PORTEC-3 trial, ensuring a reliable representation of clinical practice. In addition, the novelty of our study was enhanced by allowing a thorough analysis of attribute importance. Third, the web-based questionnaire design prevented interviewer introduced bias, facilitated response, allowed direct comparison between patients and clinicians, and provided complete data.

The main limitation of our study was the inability to include patients at the moment they were actually facing the treatment decision. Our results were clearly influenced by the preceding treatment. Selecting only disease-free patients may have reinforced this influence. Generally, patients without recurrence are more satisfied with care than patients with recurrence.[18] In addition, we did not have details on the patient's persistent symptoms, which may be influencing preference as well. Lastly, response bias may have occurred. Due to the non-random sample and the lack of information on patients who did not complete the questionnaire, we are unable to correct for this potential bias.

Clinical implications of this study are knowledge of the variability of preferences among endometrial cancer patients facing the treatment decision for adjuvant chemoradiotherapy, and of the differences between clinicians and patients. Therefore, detailed discussion about the benefits and harms are necessary to ensure their decisions are well informed and aligned with their personal values, attitudes and priorities, and not unduly influenced by clinician preferences. Clinicians tend to underestimate patients preference for less toxic treatments.[19, 20] As reinforced by this study, it is important to realize that patients might not be as willing to undergo chemotherapy as clinicians themselves. In addition, it would be important to realize that patients highly value clinicians' recommendations and that recommendations may lead people to make decisions that ultimately go against what they would otherwise prefer.[21] With the actual 5% overall survival difference in the PORTEC-3 trial[1], only 40% of the patients and 63% of clinicians would prefer adjuvant chemoradiotherapy over radiotherapy alone. Based on a survival benefit of 10% or more, adjuvant chemoradiotherapy is only advised for women with stage 3 disease and those with serous or p53 abnormal endometrial cancer.[1, 22] Our study showed that with this benefit, 57% of the patients and 84% of the clinicians would prefer adjuvant chemoradiotherapy.

Our results on attribute importance can guide patient information. It is important to point out the possibility of long-term symptoms. Patients should be informed about the expected

toxicity due to standard adjuvant pelvic radiotherapy before making a decision, even if the risk is equal when adding adjuvant chemotherapy (e.g. 36% risk of diarrhea). Although individually not significant, patients rated most negative attributes more important than clinicians. Meanwhile, clinicians seem to rate long-term tingling/numbness higher than patients. Clinicians may imagine the accompanied burden they have seen in practice resulting in higher attribute values, while the terms 'tingling', 'numbness' or 'neuropathy' might be abstract for patients without knowledge or experience. Therefore, it is important that clinicians ask about hobbies and other social activities that might be impacted and give practical examples to make it more imaginable.

In conclusion, our results showed considerable differences in minimally desired survival benefit to make adjuvant chemoradiotherapy in high risk endometrial cancer worthwhile, both among and between patients and clinicians. Overall, endometrial cancer patients desired higher survival benefits than clinicians before preferring chemoradiotherapy.

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APPENDIX A

A1. health literacy and numeracy

Health literacy

The following 3 health literacy screening questions were included:

(1) "How often do you have someone (like a family member, friend, hospital/clinic worker or caregiver) help you read hospital materials?" (Help Read);
(2) "How often do you have problems learning about your medical condition because of difficulty understanding written information?" (Problems Reading);
(3) "How confident are you filling out forms by yourself?" (Confident with Forms).

Participants were asked to choose between all of the time, most of the time, some of the time, a little of the time or none of the time. Answers were translate to a score on a scale from 0 to 4. The SNS score was calculated by summing up the three scores (range 0-12). A higher score indicates greater problems with reading.

Reference: Chew LD, Griffin JM, Partin MR et al. Validation of Screening Questions for Limited Health Literacy in a Large VA Outpatient Population. Journal of General Internal Medicine 2008; 23: 561-566.

Health numeracy

The shortened SNS-3 consisted of the following items each on a 6-point Likert scale, with interior responses labeled by numbers 2 through 5:

(1) How good are you at working with fractions? ("Not good at all," to "Extremely Good,");
(2) How good are you at figuring out how much a shirt will cost if it is 25% off? ("Not good at all," to "Extremely Good,");
(3) How often do you find numerical information to be useful? ("Never" to "Very Often,").

The first two questions focus on self-reported numeracy skills ("fractions" and "shirt"), while the third focuses on subject preference ("useful"). The SNS score was calculated by summing up the three answers (range 3-18). A higher score indicates a higher subjective rating of numeracy abilities and preferences.

Reference: McNaughton CD, Cavanaugh KL, Kripalani S et al. Validation of a Short, 3-Item Version of the Subjective Numeracy Scale. Med Decis Making 2015; 35: 932-936.

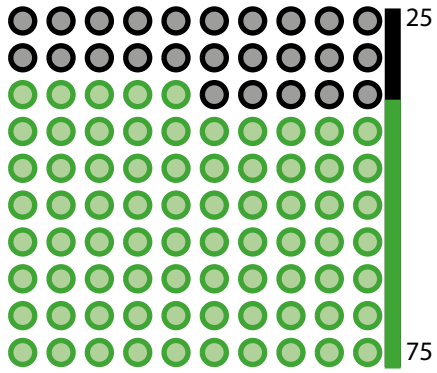
A2. treatment trade-off overview

The following overview represents the positive and negative attributes shown to participants in the treatment trade-off. After this overview with textual explanation participants had to answer the trade-off questions.

Positive attributes

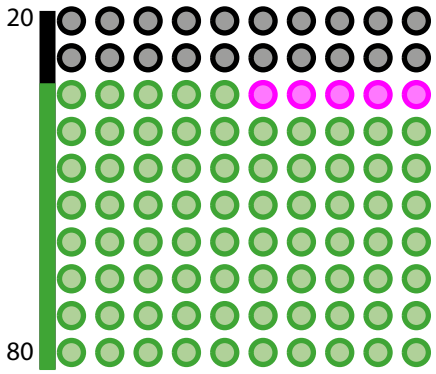
Survival benefit

Radiotherapy alone



25 out of 100 patients deceased
75 out of 100 patients alive

Chemoradiotherapy

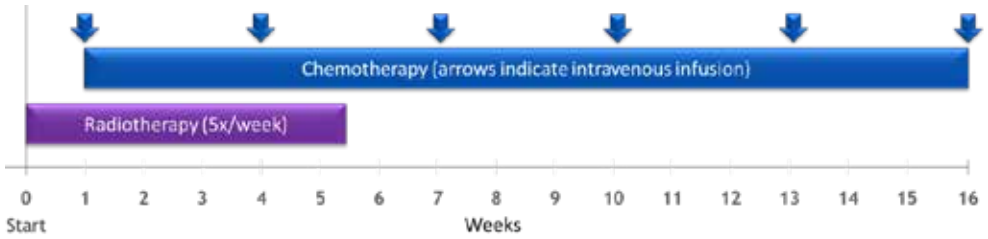


20 out of 100 patients deceased
80 out of 100 patients alive

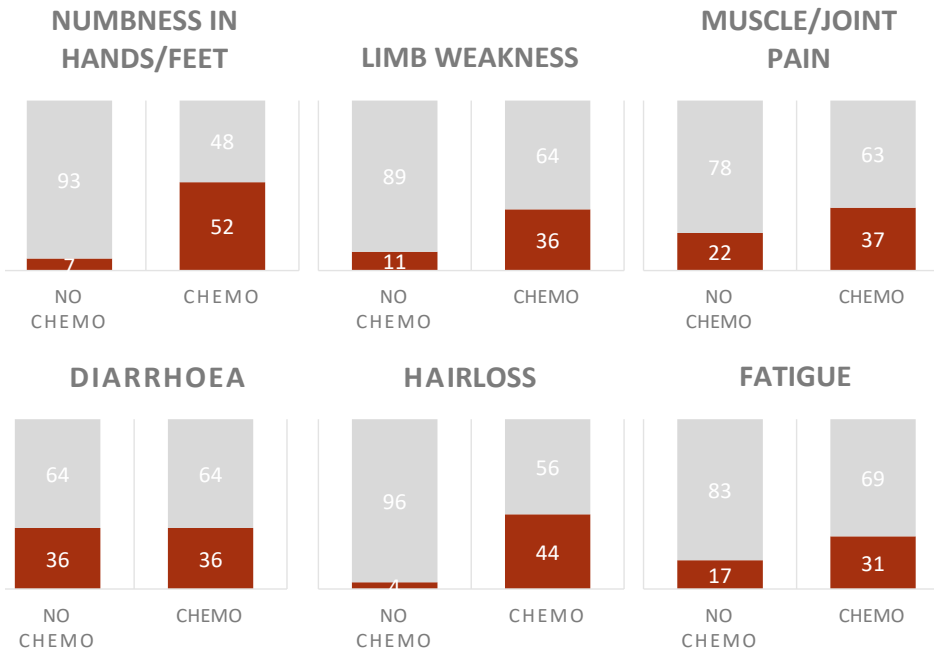
Survival at 5 years post-treatment. Green = alive; Pink = chemotherapy induced survival; Black = deceased.

Negative atributes

Treatment duration



Symptoms and functioning during and shortly after treatment



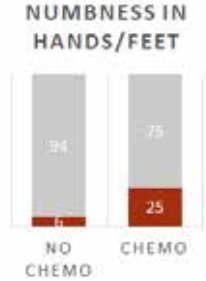
Example: During and shortly after chemotherapy, 52 out of 100 patients experienced tingling or numbness in hands and/or feet, compared to 7 patients in the radiotherapy group.

Effects on functioning and quality of life during treatment with chemoradiotherapy compared to patients treated with radiotherapy alone. Addition of chemotherapy causes:

- A small deterioration in quality of life;
- A moderate deterioration in physical functioning (exertion and daily activities);
- A moderate deterioration in social activities and family life;
- A moderate deterioration in daily activities (work/hobbies);
- No difference in memory/thinking and emotional functioning.

Long term symptoms and functioning impairments caused by CTRT

- After 3 years, 1 out of 4 patients experiences quite a bit or very much tingling or numbness in hands/feet;
- After 3 years, patients have a small decline in physical functioning;
- These symptoms have improved compared to during/shortly after treatment;
- After 3 years, other symptoms and influence on functioning have been recovered to a large extend. There are no differences between patients that did or did not receive chemotherapy.



APPENDIX B

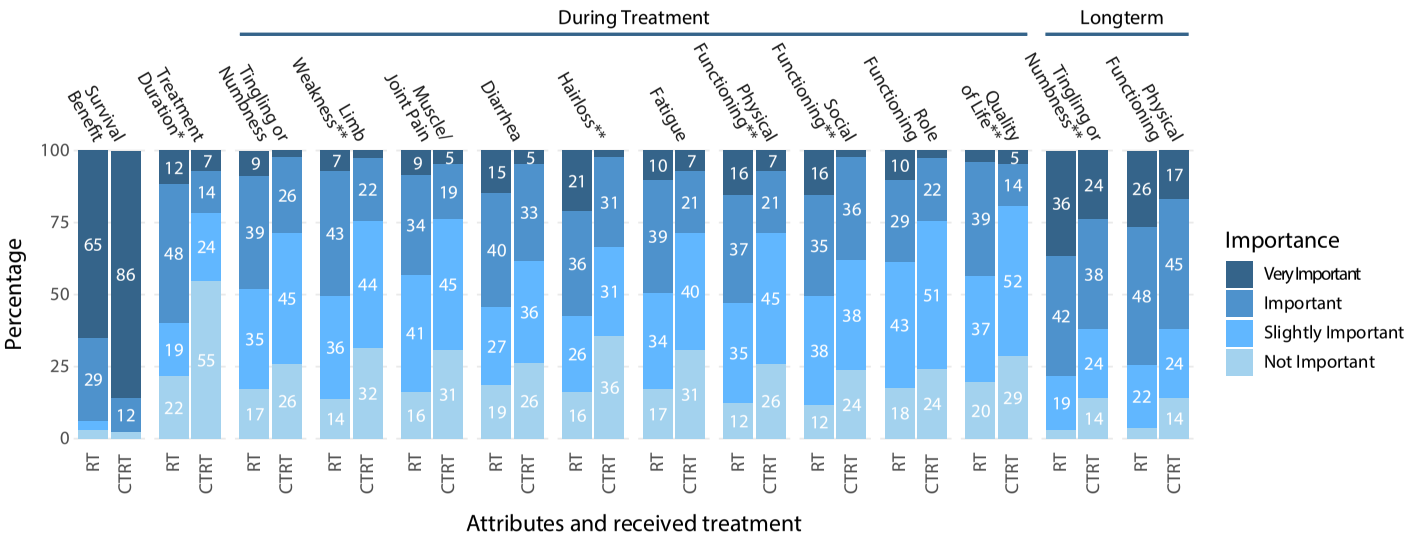


Figure B1. Attribute importance of patients who received adjuvant radiotherapy alone versus patients who received chemoradiotherapy.
CTRT = chemoradiotherapy; RT = radiotherapy.
p values less than or equal to 0.01 show significance; ***p* values less than or equal to 0.05 show a trend.

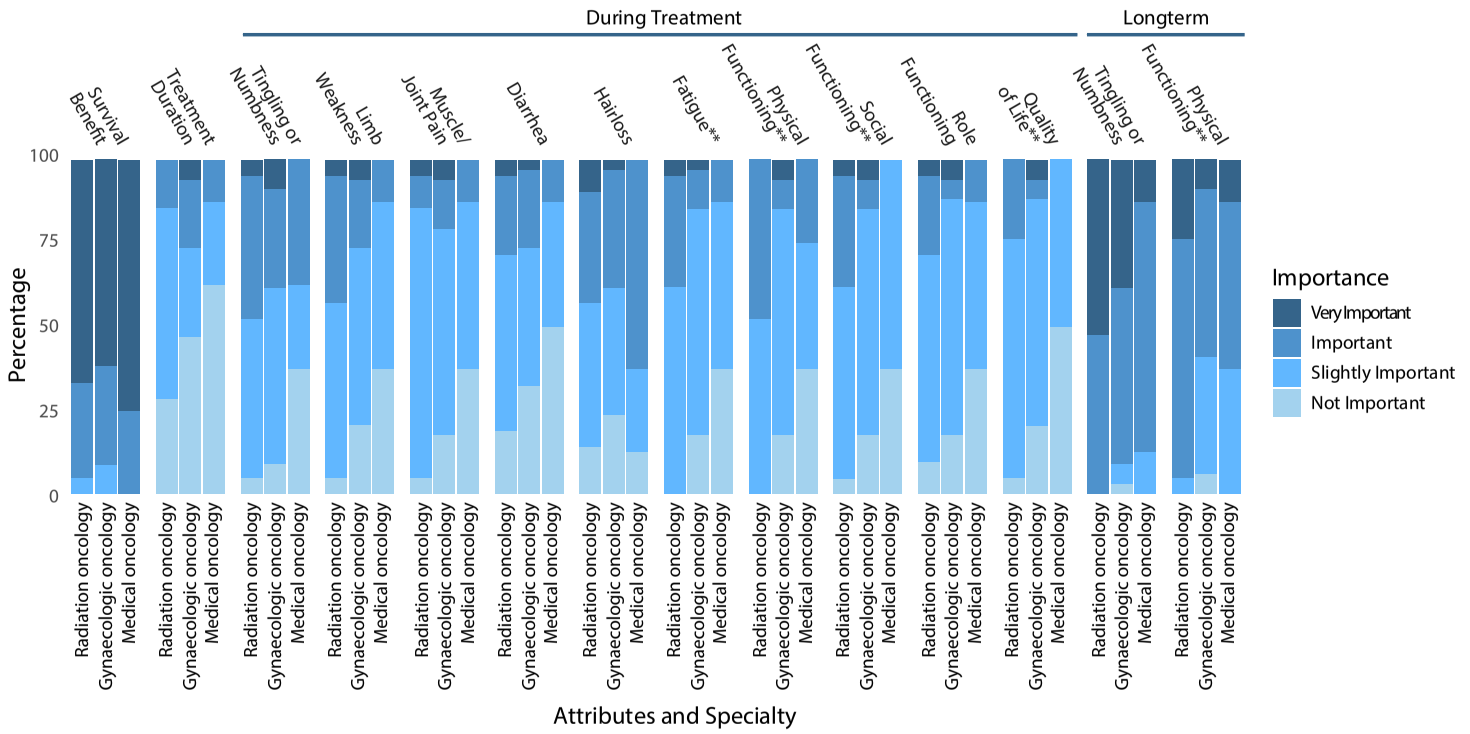


Figure B2. Attribute importance of clinicians according to their specialty: Radiation oncology, gynaecologic oncology versus medical oncology.
p values less than or equal to 0.01 were deemed significant; **p values less than or equal to 0.05 show a trend.