Patients’ and Gynecologists’ Views on Sentinel Lymph Node Procedure in Low and Intermediate Endometrial Cancer Management: A Vignette Study

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Abstract

Background: Over 200 articles about the Sentinel Lymph Node Procedure (SNP) in Endometrial Cancer (EC) have been published in the last decade, but none assesses patients’ and gynecologists’ views on this innovative technique. In this vignette study we established which factors are important for both patients and gynecologists when considering SNP in EC.

Methodology: Based on literature and interviews with patients and gynecologists a list of attributes regarding SNP was composed: 1) risk of complications of SNP, 2) chance of finding a metastasis, 3) survival gain, 4) risk of complications after radiotherapy, 5) additional operation time and 6) hospital of surgery (travel time). A questionnaire with eighteen hypothetical scenarios was developed, in which the levels of each attribute varied. Patients previously treated for low or intermediate risk EC and gynecologists with interest in oncology were invited to participate. For each scenario they were asked how strongly they would prefer SNP on a scale from 1 to 7. The strength of preference for each scenario was analyzed using a linear mixed effects model.

Results: Both patients (41/108) and gynecologists (42/126) had a preference for SNP. On the 7 point scale, the mean preference for patients was 4.29 (95% CI 3.72-4.85) and 4.39 (95% CI 3.99-4.78) for gynecologists. Patients’ preferences increased from 3.4 in case of no survival gain to 4.9 in case of three years survival gain (P=0.000), and decreased when travel time increased to over 60 min (-0.4, P=0.024), or with an increased risk of complications after adjuvant radiotherapy (-0.6, P=0.002). The chance of finding a metastasis was not important to patients. For gynecologists all attributes except travel time were significantly related to the SNP choice.

Conclusion: This study is the first to describe which characteristics are important for patients and gynecologists when considering SNP in low and intermediate risk EC management. There is a substantial variance in both patients’ and clinicians’ preferences. Individual patients make different choices highlighting the need for involving patients in decisions about adding SNP to standard EC treatment.

Introduction

Eighty percent of Endometrial Cancer (EC) patients are diagnosed at an early stage. Patients with early stage EC can be subdivided into three risk categories: low risk (endometrioid type, stage 1A, grade 1 or 2), intermediate-risk (endometrioid type, stage 1a grade 3 or stage 1B grade 1 or 2), and high risk (endometrioid type, stage 1B grade 3 and all non-endometrioid types). Standard treatment for low and intermediate risk EC consists of surgery. The indication for adjuvant therapy is based on a risk assessment, which consists of risk factors such as histological grade, myometrial invasion and the patients’ age. Lymph node status has been involved in FIGO staging since 1988. Evaluation of lymph nodes, however, is generally not part of the risk assessment, while lymph node involvement is considered to be the most important risk factor. The risk for lymph node metastases in presumed early stage EC is 15% [1-3]. As routinely performance of lymphadenectomy has not shown improvement of survival rates, while increasing the risk of treatment-related morbidity, it remains subject of discussion [4].
Worldwide several strategies for lymph node assessment are executed, varying from no lymph node dissection, to lymph node sampling in a selected patient group, complete (pelvic and para-aortal) lymph node dissection in a selected patient group to complete lymph node dissection in all EC patients. Adding a Sentinel Lymph Node Procedure (SNP) to evaluate lymph node involvement instead, might improve identification of those patients that need adjuvant therapy without performing a rigorous intervention such as a lymphadenectomy. Compared to lymphadenectomy, the SNP is associated with a relatively lower risk on complications and might lead to better staging of disease. The latter is particularly the case when pathological ultrastaging to the sentinel lymph node specimen is applied [5]. Recent studies showed that SLN procedures have high sensitivity and specificity not only in patients with low stage EC, but even in patients with high risk disease [6]. It is also shown that performing the SN procedure could lead to a higher stage of disease (upstaging) in a fair amount of patients (up until 22%) and consequently addition of adjuvant therapy (radiotherapy) to the treatment plan. However, it is still unknown if performing a sentinel node procedure impacts disease-free and overall survival [7,8].

Generally, implementation of new (surgical) techniques is primarily healthcare provider-driven. While patients are important stakeholders, their opinions regarding new techniques are rarely investigated. Despite the increasing number of papers published on SNP in EC, no studies have been done on patients’ views with regard to the introduction of this new technique. A few previous studies evaluating patients’ preferences regarding radiotherapy and EC treatment showed that heterogeneity exists among women when choosing between treatments [9,10]. Also, differences were found between patients and clinicians in minimally desired benefit from vaginal brachytherapy [9]. When determining the value of SNP in low and intermediate risk EC, it is therefore also important to take into account opinions from both gynecologists and patients.

The primary objective of this study was to determine factors that patients and gynecologists find important when considering undergoing or performing a sentinel node procedure in low and intermediate EC. Secondly, we evaluated whether there are differences in opinions between patients and gynecologists.

**Methods**

**Study design**

We studied the strength of preference for addition of the sentinel lymph node procedure to standard treatment in low and intermediate risk EC among a sample of (surviving) patients and oncology-oriented gynecologists. We used a vignette study in order to measure the relative weight of different characteristics concerning the SLN procedure in low and intermediate risk EC. Ethical approval was obtained for the study (number 2018-4040).

**Setting**

All gynecological cancers are managed in specialized gynecological oncological centers, except for presumed low stage EC, which is managed in all (regional) hospitals. Patients with early stage endometrial cancer can be subdivided into three risk categories: low risk (endometrioid type, stage 1A, grade 1 or 2), intermediate-risk (endometrioid type, stage 1A grade 3 or stage 1B grade 1 or 2), and high risk (endometrioid type, stage 1B grade 3 and all non-endometrioid types). In the Netherlands, low and intermediate risk EC is treated by total hysterectomy. Adjuvant radiotherapy (brachytherapy +/- external beam radiotherapy) is based on histological grade, myometrial invasion and the patients’ age [1]. Lymph node assessment or addition of a SNP is not part of standard care in the Netherlands.

**Questionnaire development**

A vignette is a paper case description in which patient, disease, and treatment characteristics are given [11]. The selection of relevant factors was based on a focus group with seven patients and input from three gynecologists and literature (Figure 1). In a consensus meeting the final set of six characteristics was agreed upon. All six characteristics varied at three levels (Table 1). Attempts were made for these levels to be realistic, but also to be distinctive. The levels were based on literature, consultations of experts, or if not available determined in the above-mentioned consensus meeting.

The combination of six characteristics, each consisting of three levels, resulted in 729 (36) possible scenarios. We used an orthogonal main effects design, following the methodology of the study by Koedoot and colleagues [12,13]. “It provides a subset of all possible combinations of patient and treatment characteristics and allows estimations of the relative weights for each level of the presented characteristics on the preference score” [13]. In other words, these weights are a measure for the contribution of each level to the preference score. Previous research showed that a number of 18 vignettes is feasible for participants to complete [14].

For each vignette, the respondents rated their strength of preference for addition of a SLN procedure to standard treatment on an anchored 7-point scale ranging from a strong preference against adding the SLN procedure (=1) via a neutral position, implying no preference (=4), to a strong preference in favor of adding the SLN procedure (=7).

The wording of the vignettes and feasibility of the final questionnaire was pilot tested with seven patients using the technique for improving surveys using cognitive testing and semi-structured interviews [15]. These patients were recruited through the patient advisory board for women’s cancer in our hospital. Feedback included change of wording, the order of vignettes but also the suggestions of adding a question in which patients needed to rank every factor on importance before answering the vignettes. The same vignettes were used in the questionnaire for gynecologists. This questionnaire was also pilot-tested among three gynecologists that led to some minor adjustments. An example of a vignette as presented in the questionnaire can be found in the supplemental information to this paper.

**Patients**

The patient population consisted of a retrospective cohort of surviving patients that had been treated for low or intermediate risk EC in either a large regional hospital (Rijnstate Hospital Arnhem) or at a Gynecological Oncology Centre (Radboud University Medical Centre) in the South East of the Netherlands between 2012 and 2015. Patients were included if they had been diagnosed and treated for low or intermediate risk EC. Patients who (1) had >FIGO stage 2 EC, (2) had other histological types than endometrioid EC, (3) underwent lymphadenectomy, or (4) had had recurrence of disease were excluded from the study. Background characteristics were collected from each participant, including age, height and weight, previous cardiorespiratory disease, any other type of previous surgery, stage and grade of EC, age at diagnosis, year of diagnosis and type of
Non-responding gynecologists received a reminder after two to three weeks. Non-responding gynecologists received a reminder after two and four weeks respectively.

Sample size calculation

Simulations were used for power calculations. A difference of 1 point on the 7 point outcome scale was deemed to be clinically important. These simulations assumed a 1 point difference between two levels on a single attribute, with a deviance of 1 point, and no differences on the other six attributes. Further assumptions were an overall residual deviance of 2 and a normally distributed preference with a mean of 4 and a standard deviation of 2. Under these assumptions, the before mentioned difference of 1 can be detected with a power of 80% using 50 respondents.

Data collection

Patients received a paper-based questionnaire including a return envelope and an informed consent form. Non-responding participants received a reminder after two to three weeks.

Gynecologists received a digital questionnaire using an online computer program (CASTOR EDC) using anonymous tokens so no identifiable information was collected. Non-responding gynecologists received a reminder after two and four weeks respectively.

Statistical uncertainty was expressed in 95% Confidence Intervals (CIs). The results were not corrected for physician or patient characteristics given the relatively small sample sizes.

Results

108 patients and 126 gynecologists were invited to participate in the study. 45 patients declined participation and 22 did not respond at all. 72 gynecologists (i.e. 57% of the sample) did not open the email including the invitation to the questionnaire. This resulted in 41 patients and 42 gynecologists completing the questionnaires, leading to response rates of 38% and 35% respectively. Background characteristics of both patients and gynecologists are presented in Table 2a, 2b.

Overall strength of preference for SN procedure

The mean overall preference for SNP for the 18 scenarios combined was 4.29 (95% CI 3.72 to 4.85) for patients and 4.39 (95% CI 3.99 to 4.78). On a scale from 0-7, this indicates that both the gynecologists and the patients had a slightly stronger preference for adding the SNP.
Three patients preferred SNP in all scenarios. This was never the case for the gynecologists. Four patients and one gynecologist never preferred the addition of SNP.

**Patients’ preferences**

Three variables as shown in (Figure 2) were significantly important to patients when deciding about the addition of SNP, i.e. survival gain (p=0.000) the risk of complications when radiotherapy is needed (p=0.001) and the hospital where surgery would take place (p=0.020). This is depicted in (Figure 2). For example, a patient preferred SNP more strongly when the survival gain would increase from 0 to 3 years (corresponding to an increase of 1.5 on the response scale from 1 to 7), but favored against SNP if she had to travel more than 60 minutes to another hospital (increase of 0.2 on the scale from 1 to 7).

**Gynecologists’ preferences**

For gynecologists all variables, except the hospital where the surgery needs to take place, were significantly important when deciding about SNP. As can be seen in (Figure 3), survival gain was the strongest characteristic (corresponding to an increase of 3.3 on the response scale from 1 to 7). For the probability of finding a metastasis in the SN it seemed that gynecologists did not prefer adding SNP, if the percentage of finding a metastasis was 5%, but had a stronger preference for the SNP if this probability increased above 10%.

**Discussion**

The primary objective of this study was to determine factors that Dutch patients and gynecologists find important when considering adding a sentinel node procedure in low and intermediate risk endometrial cancer. Secondly, we evaluated whether there are differences in opinions between patients and gynecologists. Both patients and gynecologists had a slightly stronger preference in favor of SNP. Gynecologists found all characteristics, except hospital of surgery, important. For patients three characteristics were relevant when choosing in favor of SNP, i.e. survival gain, the distance to the hospital where surgery would take place and the probability of complications after adjuvant radiotherapy when a positive SN was found.

Responses of patients and gynecologists had a similar trend. Patients’ responses were, however, more heterogeneous and...
reached therefore less often statistical significance than those of the gynecologists. Gynecologists were the most outspoken about the importance of survival gain. Patients found the distance to the hospital where the surgery would take place a more important characteristic than gynecologists, although it was just a small difference of 0.2 on the response scale from 1 to 7.

To the best of our knowledge this is the first study to explore patients’ and professionals’ preferences on the implementation of SNP in low and intermediate risk EC. Yet rarely done, we believe it is important to include particularly patients’ views as well when introducing new (surgical) techniques. There are some previous studies on patients’ and professionals’ preferences regarding other treatment strategies in EC. Also these studies showed that patients make different trade-offs when deciding about treatment, considering for instance oncological outcomes and impact on their quality of life.

Kim et al. [16] investigated preferences for routine lymphadenectomy versus no lymphadenectomy in early-stage EC [16]. This discrete choice experiment, including a larger number of patients, showed recurrence rate and lymphedema as statistically significant attributes impacting the preference on lymphadenectomy. They showed that patients and clinicians are willing to accept a small amount of recurrence risk to reduce the risk of lymphedema. In the study of Farrell et al. [17] studying whether women would undergo SNP or full groin lymphadenectomy in early vulvar cancer, when considering all risks and benefits: some women would choose lymphadenectomy over SNP, despite the impact on their quality of life of the first [17]. In the PORTEC-3 sub-study, concerning patients’ and clinicians’ preferences for adjuvant chemotherapy in EC, survival gain was also considered an important attribute for patients in choosing for or against adjuvant chemotherapy [10]. This mirrors results of our study showing that survival gain was the most important characteristic, among both patients and gynecologists.

The past decade a great number of studies have evaluated the value of SNP in patients with EC. It is considered feasible [5,18]; safe [19,20]; with high specificity and sensitivity [6,8]. Increasingly, adding SNP to management of EC is recommended based on these studies, particularly in countries where it would replace pelvic lymphadenectomy in low and intermediate risk EC patients [16]. In the Netherlands, women with presumed early stage low- and intermediate risk endometrioid adenocarcinoma of the uterus are treated in every (regional) hospital by total hysterectomy without assessment and surgical treatment of the lymph nodes. Based on postoperative risk assessment indicating the risk for metastatic disease, patients will receive adjuvant brachytherapy and/or external beam radiotherapy. The SN procedure would be an addition to standard care and requires certain (surgical) expertise. Previous studies on performing the SN procedure in EC and other cancers described a minimal number of 30 procedures before completion of the learning curve [21-23]. This might mean that these women might need to be referred to more specialized centers, where SNP and pathological ultrastaging can be performed. Implementation of SNP would therefore change the organization of care for women with low or intermediate risk EC in the Netherlands. It was therefore remarkable that gynecologists did not find the type of hospital where surgery needs to take place an important factor. However, other studies showed that clinicians tend to base their preferences solely on clinical factors, instead of non-clinical factors such as travel time or type of clinic.

If SNP in low and intermediate risk EC would be implemented, our results can be used to adequately counsel patients. Clinicians should be aware that patients sometimes choose against their preferences, because they also put much weight to their doctor’s recommendation [24]. Survival gain, with a 3 year range, appeared to be an important characteristic to patients. The actual impact on survival outcomes is however, not known yet [8]. Furthermore, previous research showed that in 15% of patients with low and intermediate risk EC a metastasis is detected in the sentinel lymph node [2,3,18]. These patients will receive a recommendation for adjuvant radiation therapy and better survival might be likely. Importantly, the higher the risk of complications of adjuvant radiotherapy, the less likely patients in our study were to choose for SNP. It is therefore important to inform patients that the recommendation for adjuvant therapy in the Netherlands is currently based on risk factors such as age, stage, histology, myometrial invasion and invasive growth. Consequently a number of patients without actual lymph node metastases receive radiation therapy, causing overtreatment. The SN procedure is supposed to be more specific in distinguishing which patients should receive adjuvant radiotherapy. For patients in our study the likelihood for finding a metastasized sentinel node was not important in the decision for or against SNP. On the contrary, gynecologists would not prefer adding SNP if this probability was only 5%, but would recommend in favor if this percentage would increase to 10%.

A number of limitations should be considered when interpreting our results. First, our results may be biased as only gynecological oncologists and gynecologists with a special interest in oncology were asked to participate in this study. On the otherside, when introducing SNP in the assessment of presumed low- and intermediate-risk EC these surgeons would be the ones performing the sentinel node procedures. Second, an important limitation of a vignette study is that other attributes that were not included in our study, may be
relevant as well, such as, the risk on recurrence after treatment or false negative rates. We did not include all possible characteristics because we wanted to present understandable scenarios, in which, for example, overall survival is easier to understand for patients than recurrence-free survival. We tried to prevent this potential bias by selecting the most important attributes from the literature, using the input of patients and gynecologists. Moreover, we performed a small pilot study to test the validity of our questionnaire. In this test phase, we explicitly asked whether the accompanying instructions to the questionnaire were clear. Third, the scenarios will always be hypothetical for our participants and it is unclear whether they would make other choices in real life. However, we only included women in this study who were diagnosed with and treated for low or intermediate risk EC themselves. We expect therefore that it would have been easier for them to interpret the scenarios based on their own experience. Fourth, the response rate of the patient study population was relatively low with only 38% of patients responding and less than the calculated sample size. An explanation could be its study design, in which we used eighteen vignettes. However, previous studies have indicated that respondents can handle up to seventeen choice sets [14]. A larger response rate might result in smaller intervals, but it might not necessarily change the weight of the responses [25]. In studies with larger sample sizes substantial variation in patients' views were still found [9]. Among gynecologists, a response rate of 35% was achieved. This is a reasonable response rate comparing to other surveys among health professionals. Studies with higher response rates often use a financial incentive.

Conclusion

In conclusion, our study showed that several characteristics are important when patients and gynecologists consider adding a SN procedure in low and intermediate risk EC management. Overall, patients and gynecologists’ preferences showed a similar trend, although patients were more heterogeneous and less outspoken in their preferences than gynecologists. Since patients highly value clinicians’ recommendations, they can lead to make or agree with decisions that go against what they would otherwise prefer. The importance of clinicians’ recommendations and the substantial variance in both patients’ and clinicians’ treatment preferences highlight the need for involving patients in decisions about adding a SLN procedure to standard EC treatment.

Acknowledgment

We thank the women from the Radboudumc Women’s Cancer Group who helped us designing and testing the questionnaire used in this study.

References

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