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Preferences for follow up in long-term survivors after cervical cancer

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Abstract

Introduction: An increasing number of cervical cancer survivors combined with lack of data on the efficacy of long-term surveillance, challenges existing follow-up models. However, before introducing new follow-up models, cervical cancer survivors' own views on follow up are important. We aimed to explore preferences for follow up in long-term cervical cancer survivors and their associations with self-reported late-effects.

Material and methods: In 2013, we mailed 974 Norwegian long-term cervical cancer survivors treated during 2000-2007 a questionnaire with items covering preferences for follow up after treatment, clinical variables and validated questionnaires covering anxiety, neuroticism and depression.

Results: We included 471 cervical cancer survivors (response rate 57%) with a median follow up of 11 years. In all, 77% had FIGO stage I disease, and 35% were attending a follow-up program at the time of survey. Of the patients, 55% preferred more than 5 years of follow up. This was also preferred by 57% of cervical cancer survivors who were treated with conization only. In multivariable analyses, chemo-radiotherapy or surgery with radiation and/or chemotherapy (heavy treatment) and younger age were significantly associated with a preference for more than 5 years' follow up. Late effects were reported by more than 70% of the cervical cancer survivors who had undergone heavy treatment.

Conclusions: Our study reveals the need for targeted patient education about the benefits and limitations of follow up. To meet increasing costs of cancer care, individualized follow-up procedures adjusted to risk of recurrence and late-effects in cervical cancer survivors are warranted.

KEYWORDS

cervical cancer, follow up, late adverse effects, long-term survivors, questionnaire

Abbreviations: CI, confidence intervals; OR, odds ratio.

1 | INTRODUCTION

Over the past 20 years, the 5-year survival of cervical cancer patients has increased by 4%-14% worldwide according to reports from cancer registries in 64 countries.[1] Five-year survival in Norway ranks among the highest in the world (81.4%).[2] According to current follow-up schedules in most western countries, cervical cancer patients are seen by a gynecologist for follow-up care 12-18 times within the first 5 years after primary treatment.[3] Thereafter, some women continue a long-term, even lifelong, follow up in specialist care,[3] as gynecologic oncologists tend to follow patients longer than the guidelines advise.[3] However, long-term follow up is resource-intensive, with unclear benefits for quality of life and survival for cervical cancer patients.[4,5]

Cervical cancer survivors range from women with very low risk of recurrence and low burden of late-effects to women with high burden of late-effects and/or high risk of recurrence.[6,7] There is a shift towards more individualized and needs-assessed follow up of cervical cancer patients,[8,9] and this is also debated in Norway. Prior to changing follow-up recommendations, it is important to identify surveillance preferences of cervical cancer survivors to better tailor patient information in future follow-up guidelines. Therefore, the aims of this study were to explore the prevalence and the determinants of preferences for long-term (>5 years) follow up in a sample of Norwegian cervical cancer survivors. Further, we explored the associations between presence of late-effects and preferences for long-term follow up.

Key message

Of a cohort of long-term cervical cancer survivors, 55% preferred long-term (>5 years) follow up. Heavy treatment and younger age at survey were associated with the preference for long-term follow up. Cervical cancer survivors should be educated about the limited evidence of lifetime follow up.

2 | MATERIAL AND METHODS

2.1 | Patients

Patients with cervical cancer diagnosed between 1 January 2000, and 31 December 2007 who were treated at hospitals located in the Health Regions of South Eastern Norway and Northern Norway, were identified in the Norwegian Cancer Registry. Inclusion criteria were 18-76 years of age at survey, ability to read Norwegian, no history of second cancer, considered tumor-free and not on any cancer treatment as of 31 December 2012. Eligible patients received a letter containing study information, a consent form and the survey questionnaire. Non-responders received one reminder.

2.2 | Organization of follow up

After treatment, Norwegian cervical cancer patients participate in a standard routine follow-up schedule according to the Norwegian national guidelines.[10] The follow-up schedule recommends visits at a gynecological department three to four times annually the first 2 years, twice a year over the next 3 years, and annually thereafter depending on the recommendations of the clinician. The follow-up visits are usually conducted by gynecology specialists or gynecologic oncologists.

2.3 | Description of dependent variables

In the absence of a single, suitable, validated questionnaire on long-term follow up after cervical cancer, relevant questions were developed by our research group (Table S1). For this purpose, studies of cancer survivors' views on cancer follow up were reviewed and we included relevant issues identified in these studies.[11,12] The questionnaire was thereafter piloted in eight cervical cancer survivors and five healthy women, and modified according to their feedback. In the present study (n = 471), the Kuder–Richardson reliability coefficient was 0.71 for the late-effects subscale. Late effects experienced by fewer than 5% of the cervical cancer survivors (ie coronary heart disease, osteoporosis and second cancer) were not included in the analyses.

2.4 | Demographic and clinical characteristics

A non-paired relationship described women not married or cohabiting. Low level of education was categorized as ≤12 school years completed vs high level of education (>12 years). Comorbidity was based on self-reported myocardial infarction, diabetes, chronic obstructive lung diseases, hypertension, rheumatic diseases (all 1 point) and kidney disease (2 points) based on illness points according to Charlson et al.[13] Self-rated health had five response alternatives and was dichotomized into good (excellent/very good/good) and poor (fair/poor).

Information on age, histology, International Federation of Gynecology and Obstetrics (FIGO) stage and previous treatment was obtained from the medical records. The patients were treated according to Norwegian guidelines[14] and divided into four treatment groups as described in a previous publication.[15] Group 1 was treated with conization. Group 2 was treated with major surgery in terms of radical hysterectomy with pelvic lymph node dissection with or without bilateral salpingo-oophorectomy. Group 3 was treated with external-beam pelvic radiation to the tumor and the regional lymph nodes, combined with brachytherapy, and concomitant low-dose cisplatin-containing chemotherapy (chemo-radiotherapy). A small subsample received neoadjuvant

chemotherapy followed by standard major surgery (Group 4a). A few other patients had combinations of surgery and chemo-radiotherapy (Group 4b). Due to small sample sizes, the Groups 4a and 4b were merged into one group (Group 4) of surgery combined with either chemo-radiotherapy and/or neoadjuvant chemotherapy. Patients who received treatment for recurrence were allocated to the respective treatment group depending on treatment modality irrespective of primary treatment. As radiation therapy tends to cause more late-effects than surgery,[6,7] we compared women treated with surgery only (Groups 1 + 2) vs those with more extensive treatment (Groups 3 + 4).

2.5 | Neuroticism

Neuroticism was self-rated on an abridged version of The Eysenck Personality Inventory[16] with six items concerning personality characteristics. The sum score ranged from zero to six, and was dichotomized into the high (sum score 3-6) and low neuroticism (sum score 0-2) group according to the procedure used in the third Health Study of North-Trøndelag County.[17]

2.6 | Anxiety

The Hospital Anxiety and Depression Scale comprised seven items each on the anxiety and depression subscales rated for the last week. The item scores ranged from 0 (not present) to 3 (highly present), so the subscale scores ranged from 0 (low) to 21 (high). Only the anxiety subscale was adopted, and Cronbach's alpha was 0.66.[18] Cases of potential clinical anxiety disorder were defined by a score of ≥8 on the anxiety subscale.[18]

2.7 | Depression

The Patient Health Questionnaire-9 contained nine items covering depression for the last 2 weeks, and each item was scored from 0 (not at all) to 3 (nearly every day), providing a 0-27 severity score.[19] Cronbach's alpha was 0.87 in the sample. Cases of potential clinical depression were defined by a score of ≥10.[19]

2.8 | Statistical analyses

Descriptive statistics was used to present demographic and clinical characteristics of the sample. Continuous variables were described with median and range, and categorical variables with numbers and percentages. The internal consistencies were examined with Cronbach's coefficient alpha and Kuder-Richardson Formula 20 for dichotomous variables. Associations between independent variables and preference for more than 5 years of follow up as dependent variable (no preference for more than 5 years follow up as reference) were examined with multivariable logistic regression analysis. The strength of associations was estimated as odds ratios (ORs) with 95% confidence intervals (95% CI). Variables considered clinically relevant were tested for multicollinearity and then included in the multivariable analysis. We only included late-effects that differed significantly between cervical cancer survivors who preferred more vs less than 5 years of follow up in the model. The tests were two-sided and $P < .05$ were considered statistically significant. Analyses were performed using Statistical Package for the Social Sciences version 24 (IBM Corp., Armonk, NY, USA).

2.9 | Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics of South East Norway (#2013/634). The cervical cancer survivors included in the study provided their written informed consent.

3 | RESULTS

In total, 822 (South Eastern Health Region) and 152 (Northern Health Region) cervical cancer survivors were invited to participate in the survey. Non-responders were sent one reminder, and 11 survivors could not be located. A completed questionnaire were returned by 546 of 963 women (57% response rate). Thirty-five patients were excluded (22 due to another self-reported cancer, 40 patients due to recurrence of disease and 13 due to missing responses to the follow-up items). Accordingly, 471 cervical cancer survivors were included in the study analysis. Demographic and clinical characteristics of the participants are summarized in Table 1.

3.1 | Preference for long-term follow up

Of the cervical cancer survivors, 55% (n = 259) preferred long-term follow up (Table 1); 52% of them were attending regular follow-up visits at the time of the survey, a median time of 11 years (range 6-15) since diagnosis. In contrast, 212 survivors (45%) reported no need for long-term follow up, although 11% were still attending regular follow up. Significantly more women in treatment Groups 3 + 4 (hereafter "heavily treated") preferred long-term follow up compared with the surgery group ($P = .007$). However, 57% in treatment Group 1 (conization) preferred long-term follow up and 29% attended regular follow-up visits at the time of the survey.

In the multivariable logistic regression analysis, heavy treatment and younger age were significantly associated with the preference for long-term follow up (Table 2).

Regarding the preferred level of care providing follow up, 69% of the cancer survivors preferred a gynecologist (59% gynecologists at hospitals, 10% gynecologists in private practice) and 2% a general

TABLE 1 Characteristics of long-term cervical cancer survivors and their preference for long-term follow up

	Preference for >5 y follow up (n = 259)	No preference for >5 y follow up (n = 212)	*P* value	Total sample, n = 471
Age at diagnosis (y), median (range)	40 (23-66)	42 (24-68)	.49	41 (24-68)
Age at survey (y), median (range)	51 (32-75)	54 (33-76)	.46	53 (32-76)
Histology, n (%)				
Squamous cell carcinoma	185 (71)	162 (77)	.59	347 (74)
Adenocarcinoma + other non-squamous cell carcinoma	69 (27)	45 (21)		114 (24)
Unknown	5 (2)	5 (2)		10 (2)
FIGO stages, n (%)				
Stage 1A	80 (31)	83 (39)	.37	163 (35)
Stage 1B	113 (43)	86 (41)		199 (42)
Stage 2	49 (19)	35 (16)		84 (18)
Stage 3	10 (4)	6 (3)		16 (3)
Stage 4	4 (2)	0		4 (1)
Unstaged	3 (1)	2 (1)		5 (1)
Treatment, n (%)				
Conization	48 (19)	36 (17)	.01	84 (18)
Major surgery[a]	107 (41)	116 (55)		223 (47)
Chemo-radiotherapy	60 (23)	41 (19)		101 (21)
Major surgery + radiation and/or chemotherapy	44 (17)	19 (9)		63 (14)
In paired relationship, n (%)	183 (71)	140 (66)	.28	323 (69)
Level of education, n (%)				
Low (<12 y)	134 (52)	128 (60)	0.07	262 (56)
High (≥12 y)	125 (48)	84 (40)		205 (44)
Comorbidity index, n (%)				
0 point	188 (72)	142 (67)	.054	330 (70)
1 point	59 (23)	48 (23)		107 (23)
≥2 points	12 (5)	22 (10)		34 (7)
Daily smoking, n (%)	53 (21)	39 (18)	.57	92 (20)
Poor self-rated health	63 (24)	49 (23)	.71	112 (24)
Anxiety sum ≥8, n (%)	140 (54)	114 (54)	.95	254 (54)
Neuroticism score ≥3, n (%)	104 (40)	78 (37)	.54	182 (39)
Depression score ≥10, n (%)	46 (18)	39 (18)	.91	85 (18)

[a]Major surgery: radical hysterectomy with pelvic lymph node dissection with or without bilateral salpingo-ophorectomy.

practitioner, and 29% stated that the quality of follow up was more important than the profession of the provider.

3.2 | Self-reported late-effects

Late-effects were most frequently reported in treatment Groups 3 + 4 (Figure 1). Furthermore, 83% of the women in treatment Group 4 reported multiple late-effects compared with 31% in treatment group 1 (Figure 2). Cervical cancer survivors in treatment Groups 3 + 4 reported significantly more intestinal problems ($P < .001$), urinary problems ($P < .001$), sexual problems ($P < .001$), and fatigue ($P < .001$) (Figure 1). Lymph edema was associated significantly more ($P < .001$) with surgery (treatment Groups 2 + 4), and 44% women reported this problem in treatment Group 4, compared with 29% in treatment Group 2. In the total sample, anxiety and depression scores indicated that 54% of women had an anxiety disorder and 18% a depression disorder (Table 1). There were no significant differences in self-reported late-effects between women who preferred long-term follow-up care and those who did not (Table 3).

4 | DISCUSSION

To our knowledge, this is the first study to investigate preferences for long-term follow up among recurrence-free long-term cervical

TABLE 2 A multivariable logistic regression model of associations between clinical characteristics and preference of long-term follow up in cervical cancer survivors

Variables	OR	95% CI	*P* value
Age at diagnosis	1.02	1.00-1.04	.035
Education >12 y	1.45	0.97-2.18	.072
Treatment Group 3 + 4	2.06	1.32-3.21	.001
Poor self-rated health	0.92	0.60-1.41	.71
Comorbidity			.06
0 point (reference)	1.00	—	—
1 point	1.08	0.65-1.67	.74
≥2 points	2.43	1.16-5.06	.02
HADS-anxiety[a]	0.98	0.68-1.41	.92
Neuroticism	0.89	0.61-1.29	.54
PHQ depression[a]	1.03	0.64-1.65	.91

[a]HADS-Anxiety and PHQ-9 Depression correlated moderately with Spearman's coefficient rho 0.30.

cancer survivors. At a median of 11 years after diagnosis, a majority (55%) of the survivors preferred more than 5 years of follow up. Heavy treatment and younger age were associated with a preference for long-term follow up in the multivariable analyses. Women with heavier treatment experienced more late-effects than those treated with surgery only. However, presence of late-effects were not significantly associated with a need for long-term follow up in the analyses.

As shown in a review study on patient preferences for follow up after cancer, patients appear to lose confidence in their bodies and fear cancer recurrence even after treatment for low-risk cancer.[20] Further, after treatment, the patients find regular visits important to reassure them that they have no recurrence, as they expect recurrences to be detected at the follow-up visits.[20,21] This may explain the need for more than 5 years follow up among the majority of the survivors. In the multivariable modeling, we found an association between heavy treatment and a preference for long-term follow up. A possible explanation is that patients with higher-risk tumors are likely to receive heavy treatment and consequently be recommended long-term follow up, which may influence their preferences 5 years after treatment. As expected, women with heavy treatment reported more late-effects compared with those treated with surgery only. On the other hand, late-effects were not associated with a preference for long-term follow up, suggesting that this is not the reason why heavy treatment is associated with a preference for long-term follow up. However, there was a tendency towards more hormonal changes (P = .07) and intestinal problems (P = .08) among those who preferred long-term follow up. As shown in Figure 1, intestinal and urinary late-effects, as well as sexual late-effects and lymph edema were the most frequently reported among the participants, which is in line with the literature.[22]

The prevalence of self-reported anxiety (54%) and depression (18%) among the cervical cancer survivors in our study is similar to findings in other studies of long-term cervical cancer survivors.[23,24] However, we did not find any association between preferences for longer follow up and depression, anxiety and personality traits such as neuroticism.

The participants preferred follow-up care to be performed by hospital specialists, which has been reported before.[21] This may be explained by the fact that most follow-up visits are performed in hospitals and that patients tend to favor the existing service. In a study on the attitudes of gynecological cancer survivors towards follow up, those who had not yet started follow up were more willing to be followed up by a general practitioner, as opposed to those who had attended hospital follow up for longer time, who preferred hospital specialists.[21]

The purposes of cancer follow up are to detect recurrences that are amenable to treatment providing cure or long-term survival, to detect and treat early- and late-effects, and to offer psychological support after treatment.[25] Whether routine surveillance for early detection of recurrence with distant metastases improves cervical cancer survival is not documented.[26] However, patients with local recurrences may be candidates for curative radiation[27] or, in rare cases, for pelvic exenteration with curative intention.[28] Approximately 80% of recurrences of cervical cancer occur within 2-3 years after treatment,[26,29] and the value of continued follow up is debated.[5] There is evidence that routine visits can induce stress during follow up,[30] and many gynecological cancer survivors report anxiety before and relief after the visits, based on fear of a recurrence that will most likely

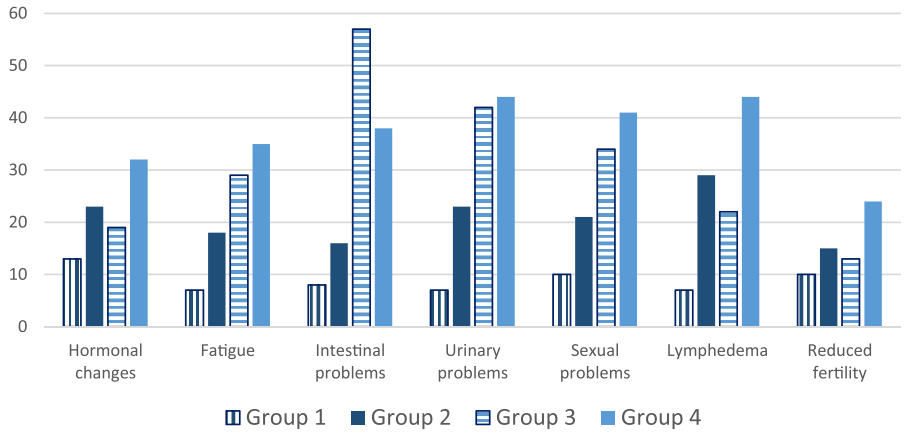

FIGURE 1 Self-reported late-effects in four treatment groups reported as percentage within each group [Color figure can be viewed at wileyonlinelibrary.com]

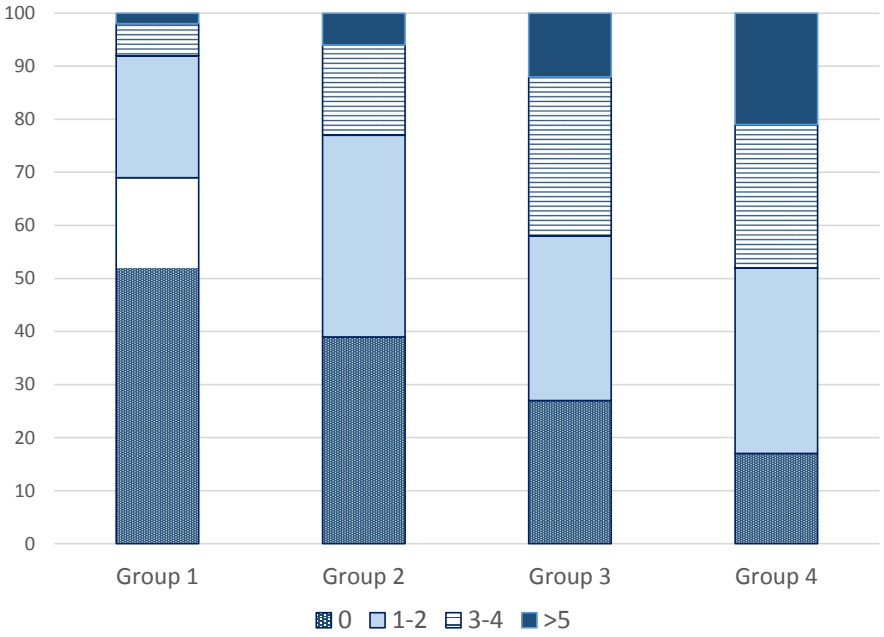

FIGURE 2 Number of self-reported late-effects in four treatment groups [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Self-reported late-effects in long-term cervical cancer survivors

	Preference of long-term follow up, (N = 259) n (%)	No preference of long-term follow up, (N = 212) n (%)	*P* value
Hormonal changes	64 (25)	38 (18)	.07
Reduced fertility	45 (17)	25 (12)	.09
Chronic fatigue	59 (23)	39 (18)	.24
Intestinal problems	77 (30)	48 (23)	.08
Bladder problems	73 (28)	55 (26)	.59
Sexual problems	70 (27)	44 (21)	.11
Lymphedema	67 (26)	54 (26)	.92

never occur.[30] In the present study, 57% of the cervical cancer survivors treated with conization preferred long-term follow up. This was unexpected, as this group of patients both has an excellent prognosis and reports low levels of late-effects. One reason may be lack of information on the limited evidence of long-term follow up effects on overall survival. Another reason may be the clinician's difficulties in terminating follow-up care. Our findings imply that targeted information at the end of treatment on the benefits and limitations of routine follow up is important, letting the patients know what to expect from the follow-up care. Through shared decision making, it important to plan how long the routine visits will continue. Given that most recurrences occur within 3 years after treatment[26,29] and that follow-up visits are time-consuming and expensive for both the patient and the clinician, the value of continued follow up for more than 3 years in a hospital setting is debatable, especially in low-risk cervical cancer survivors. New models for follow-up care are emerging and one of the models proposed is a risk-stratified follow-up model where cancer survivors are stratified into low, moderate or high-risk based on risk of recurrence and expected late-effects.[25]

A strength of our study is the use of validated self-rating instruments with established psychometric properties, apart from the questionnaire on preferences for follow up. However, the latter was piloted before being utilized in the study. Another strength is the population-based recruitment from two of Norway's five health regions with the highest incidence of cervical cancer in Norway.[2] A limitation of our study is the lack of assessment of details of preferred follow up such as frequency of routine visits, and the number of years they had attended routine follow up since end of treatment. Further, we did not assess physician factors related to long-term follow up. Though our response rate of 57% at a median of 11 years post diagnosis is acceptable, the external validity of our findings may have been compromised by respondent selection bias, and it is unclear how this would affect preference estimates for follow-up care strategies. In addition, lack of data allowing for an attrition analysis characterizing the non-respondents is a limitation. Finally, since we only have cross-sectional data, we can only present significant associations between variables, rather than causal findings.

5 | CONCLUSION

Our study highlights that cervical cancer survivors need to be educated about the effectiveness of follow-up examinations and the limited evidence for lifetime follow up. Long-term follow up of low-risk non-symptomatic cervical cancer survivors may support an unnecessary fear of cancer recurrence. While efforts are ongoing to improve cervical cancer survivors' long-term prognosis, it should be

possible to create more individualized follow-up programs adjusted to risk of recurrence and late-effects in cervical cancer survivors.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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