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Quality of life in long-term cervical cancer survivors: A population-based study

Gwenael Le Borgne [a,*], Mariette Mercier [a,b], Anne-Sophie Woronoff [c], Anne-Valérie Guizard [d], Edwige Abeilard [d], Agnès Caravati-Jouvenceaux [a], Delphine Klein [e], Michel Velten [e,f], Florence Joly [g]

[a] University of Franche-Comté, Department of Biostatistics, UPRES EA 3181, Besançon, France
[b] University Hospital Jean Minjoz, Quality of Life and Cancer Plateform, Besançon, France
[c] University Hospital Jean Minjoz, Doubs and Belfort Territory Cancer Registry, Besançon, France
[d] François Baclesse Comprehensive Cancer Center, Calvados Cancer General Registry, Caen, France
[e] University of Strasbourg, Department of Epidemiology and Public Health, Bas-Rhin Cancer Registry, Strasbourg, France
[f] Paul Strauss Comprehensive Cancer Center, Strasbourg, France
[g] University Hospital Côte de Nacre, François Baclesse Comprehensive Cancer Center, Medical Oncology Department, Inserm 1086, Caen, France

HIGHLIGHTS

- Fifteen-year cervical cancer survivors express more psychological distresses than healthy controls.
- High level of lymphedema reported 15 years after diagnosis.
- Adjuvant radiotherapy significantly affected quality of life.

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ABSTRACT

Objectives. To assess long-term quality of life (QOL) in cervical cancer survivors (CCSs), 5, 10, and 15 years after diagnosis.

Methods. In a cross-sectional population-based study, CCSs diagnosed in 1990, 1995, or 2000 were randomly selected from 3 tumor registries in France. Healthy controls were randomly selected from electoral rolls, stratifying on age group and residence area. Five QOL questionnaires (SF-36, EORTC QLQ-C30, the cervical cancer-specific module (EORTC QLQ-CX24), the MFI fatigue questionnaire, the STAI for anxiety) and a life condition questionnaire were used. Analysis of variance was used to compare QOL scores of survivors by period of diagnosis (5, 10, and 15 years) with those of controls and according to treatment modality, adjusted for socio-demographic data.

Results. A total of 173 localized CCSs (42% treated with surgery alone and 58% with a combination of treatments) and 594 controls participated in the study. Compared with controls, CCSs expressed globally similar good QOL, except for impaired psychoemotional domains in 15-year survivors ($p<0.01$). Worsening of some symptoms was observed over time, 15-year survivors in particular reported significantly more lymphedema than 5-year ($p=0.0009$) and 10-year CCSs ($p=0.002$). Compared with CCSs treated by surgery alone, QOL of CCSs who received radiotherapy was significantly more affected in terms of cervical cancer specific problems, such as sexual dysfunction ($p=0.002$), voiding and abdominal symptoms ($p=0.01$), and lymphedema ($p=0.01$).

Conclusions. Even after 15 years, QOL of CCSs is impacted in psychological domains, compared with healthy controls. Among CCSs, women treated by adjuvant radiotherapy expressed more physical sequelae.

Introduction

Cervical cancer (CC) was the third most commonly diagnosed cancer in women worldwide in 2008, and the majority of these cases occur in developing countries [1]. In France, CC is the twelfth most frequent among cancers in women, with an estimate of almost 3000 new cases for 2011 [2]. Peak incidence was estimated in women aged 40 years in 2005 [3]. Due to earlier detection thanks to wider screening and more effective treatment, 5-year relative survival is currently estimated at 70% in France, [4]. Localized CC is a curable disease, with a 5-year relative survival of 91.5% [5]. Therapeutic management of CC must take into account the stage of the disease, general health, sexuality and fertility of the patient. Indeed, depending on the chosen treatment strategy (surgery, radiotherapy, brachytherapy, chemotherapy, alone or in combination), several complications may appear in the short and long-term, such as urinary problems, lower limb lymphedema, vaginal dryness or dyspareunia, and induced

* Corresponding author at: Department of Biostatistics, UPRES EA 3181, Faculty of Medicine, University of Franche-Comté, 2 Place Saint-Jacques, 25030 Besançon, France. Fax: +33 3 81 66 52 99.
E-mail address: gwen2502@hotmail.fr (G. Le Borgne).

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menopause [6–8]. Therefore cervical cancer survivors (CCSs) will live with the physical and psychological sequelae of the disease and treatment for a long time after diagnosis. Consequently, it is important to examine the impact of both the disease and the treatment on the long-term quality of life (QOL) of these women. Few studies have assessed long-term QOL in these patients to date [6–8]. Only one recent population-based study evaluated QOL in patients with CC 10 years after diagnosis [7]. Moreover, in most studies, the number of patients included is low, and few compared results to the general population.

We conducted a multicenter population-based study among patients randomly selected from the French regional cancer registries of three Departments, namely, Calvados, Doubs, and Bas-Rhin, to compare long-term QOL of CCSs 5, 10, and 15 years after diagnosis with QOL of healthy controls.

Materials and methods

Study design and recruitment

A cross-sectional descriptive survey of CCSs was performed. All the survivors were randomly selected from files of three population-based cancer registries in the Bas-Rhin, Calvados and Doubs Departments of France. These three cancer registries cover a total of 2.2 million inhabitants, representing 3.5% of the French population.

Patients were eligible if they had developed non distant metastatic CC only (carcinoma in situ excluded), were disease-free (i.e. not under treatment for a period $\geq$5 years after diagnosis), and were able to provide written informed consent.

To evaluate the effect of time on QOL, cases were selected among patients diagnosed in 1990, 1995, or 2000.

CCSs were compared with controls randomly selected from electoral rolls of the three areas covered by the cancer registries and who had no prior history of cancer (after checking the registry database), with stratification on age ($\pm$10 years) and residence area (urban, $\geq$2000 inhabitants or rural, <2000 inhabitants) at the time of the survey. At least 2 controls were selected per patient for each survival period (5, 10 or 15 years).

Collected data

Participants (patients and controls) completed standardized validated in French language instruments assessing QOL, fatigue and anxiety, and a living condition questionnaire.

The Medical Outcomes Study 36-item Short Form Health Survey (SF-36) measures general QOL and contains eight functional scales exploring physical, social and mental dimensions [9–12].

The European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire, QLQ-C30, is a 30-item questionnaire assessing the general QOL of cancer patients. It measures global health, 5 functional domains (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and 6 symptom or problem single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems) [13,14].

The cervical cancer specific module of the EORTC (QLQ-CX24) was sent only to CCSs. It contains three multi-item scales (symptom experience, body image, and sexual/vaginal functioning) and six single-item scales (lymphedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity, and sexual enjoyment) [15].

Anxiety was assessed using the French version of the Spielberger State Anxiety Inventory (STAI). The global score was calculated as the sum of 20 items measuring the level of present anxiety [16].

Fatigue was evaluated using the French version of the Multidimensional Fatigue Inventory (MFI-20). It is a 20-item questionnaire measuring 5 aspects of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue [17–19].

A linear transformation was used to standardize raw scores to a 0–100 scale. For functional scales, higher scores indicate better perceived health. For symptom scales, higher scores indicate a higher level of problems.

In addition to the aforementioned questionnaires, we also collected information about family, social, professional status, and comorbidity using a questionnaire for living conditions used in previous surveys [20,21]. This questionnaire included items on education level, marital status, number of children, leisure occupations, life insurance problems, employment, use of medical services, and familial and social relationships. Prior to the survey, the five questionnaires were tested on 30 subjects (15 cases and 15 controls—10 per registry area) not subsequently enrolled in the study population.

For cases, clinical data (date of diagnosis, tumor extension (FIGO stage), surgery, radiotherapy, chemotherapy, and recurrence) was retrieved from medical records.

Procedure

The project was approved by the Ethics Committee of the University Hospital of Besançon (Doubs, France) as well as by the National French Data Protection Authority (CNIL). In 2007, selected subjects were mailed a package including a letter presenting the aim of the study signed by either their physician from the medical department where the patients had been treated for cancer, or, for controls, by the co-investigator in charge of the study in the registry area; the survey instruments; an informed consent form; and a postage-paid return envelope. A reminder was mailed after 1 month when necessary.

Statistical analysis

Descriptive analysis was performed using the Chi-square test for categorical variables and the Kruskal–Wallis non parametric test for the QOL scores. In order to identify socio-demographic variables significantly linked to QOL scores, we performed a multivariate analysis of variance in controls only, separately for each QOL instrument, considering the controls to be representative of the general population. Age class, employment status, education level, marital status, comorbidities, monthly income and hospitalization during the last 12 months significantly influenced most of the scales. Then, we performed an analysis of variance on both cases and controls in order to compare QOL scores between cases and controls, adjusting for the socio-demographic variables found to be significantly linked to scores in the previous step. Considering the study design, the stratification variables: registry area, place of residence (urban vs. rural) and age class (four categories) were systematically introduced as adjustment variables. A four-level categorical variable to compare each of three survivor groups with controls was created.

Two-sided tests were used in reporting the results. To account for the number of tests performed, the significance level was set at 0.01 for all tests. For the clinical significance of QOL scores, we relied on the values generally in use, based on work by Osoba et al. [22]: i.e. a difference of 5 to 10 units (on a scale ranging from 0 to 100) was considered as small, from 10 to 20 it was considered as moderate, and a difference greater than 20 was considered as large. Missing data for component items of QOL scores were treated according to published recommendations. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Power considerations

Based on the variability of scores reported in previous QOL studies, our study was designed to be able to detect a difference of $\geq$10 points on a scale of 0 to 100, when the standard deviation of the difference was equal to 40 (in a matched setting with two controls per case). With an alpha risk of 0.01 and 90% power, we calculated that 240