Socioeconomic status as an independent risk factor for severe late bowel toxicity after primary radiotherapy for cervical cancer ☆

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HIGHLIGHTS

- 1/8 women develop severe late bowel toxicity after radiotherapy for cervical cancer.
- Severe late bowel toxicity occurs mostly within the first 3 years after treatment.
- Early diagnostics and adequate management of acute bowel toxicity is warranted.

GRAPHICAL ABSTRACT

ARTICLE INFO

ABSTRACT

Objective. To evaluate the frequency of and risk factors for severe late bowel toxicity after curative radiotherapy in women treated for locally advanced cervical cancer.

Methods. Included were 515 women treated for locally advanced cervical cancer with primary radiotherapy with curative intent from 1992 to 2013. Bowel toxicity was graded according to the Common Terminology Criteria for Adverse Events. Associations between risk factors and severe late bowel toxicity were assessed using Cox proportional hazards regression models.

Results. Median follow-up was 78 months. Fifty-nine patients developed severe late bowel toxicity. The actuarial 3-year and 5-year severe late bowel toxicity rates were both 13%. In the multivariable analysis, factors significantly associated with severe late bowel toxicity were: smoking (HR 2.59 [1.48–4.55]), severe acute bowel toxicity (HR 2.46 [1.24–4.49]), previous major abdominal surgery (HR 2.35 [1.20–4.60]), hypertension (HR 2.33 [1.23–4.40]), parametrial boost (HR 2.18 [1.10–4.33]), low socioeconomic status (HR 2.05 [1.17–3.59]) and low BMI (HR 0.93 [0.88–0.99]). First symptoms of severe late bowel toxicity were reported after a median follow-up of 9 months, but occurred up to 10 years after end of treatment. Only one third of the patients with severe late bowel toxicity were referred to a gastroenterologist.

Conclusions. Severe late bowel toxicity is a frequent complication of definitive radiotherapy for cervical cancer. Several independent risk factors were found which warrant further research. A standardized and structured approach in the early diagnostics and management of bowel toxicity is needed.

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1. Introduction

The improved long-term survival after treatment for locally advanced cervical cancer has led to an increase of women exposed to the late side-effects of radiotherapy [1,2]. New treatment modalities, including intensity-modulated radiotherapy (IMRT), 3-dimensional adaptive brachytherapy and the use of interstitial needles, have allowed tumor dose escalation while limiting exposure to the surrounding organs [2–4]. Nevertheless, radical cancer treatment invariably leads to damage of healthy tissue.

Gastrointestinal complaints are among the most common and debilitating symptoms of chronic pelvic radiation disease [5,6]. In patients with locally advanced cervical cancer, data on the incidence of severe late bowel toxicity (SLBT) vary widely [7,8]. Up to 90% of survivors of cervical cancer have permanent alterations of their bowel habits [9]. For about half of these women these symptoms have a negative impact on quality of life [9]. Moreover, SLBT is often chronic and can cause perpetual impairment in the ability to perform daily and occupational tasks.

Many risk factors for SLBT after pelvic radiotherapy have been described. However, the results of former studies were inconsistent and limited by suboptimal methodology or small samples sizes. Suggested patient-related risk factors include: low body mass index (BMI) [10–12], higher age at diagnosis [13], previous abdominal surgery [12,14], hypertension [12], diabetes mellitus [15] and smoking [10]. Suggested treatment-related risk factors include: 3-dimensional conformal radiotherapy (compared to IMRT) [3], concurrent chemoradiation [16], external beam parametrial boost [17], higher dose to the rectum [13,14,18] and extended para-aortic field radiotherapy [19,20].

A recently published prospective multi-cohort study showed that low socioeconomic status (SES) is associated with a reduction in life expectancy [21]. The association between SES and toxicity after gynecological cancer is however currently unknown in literature.

The aim of the present study was to investigate the frequency of and risk factors for SLBT after primary radiotherapy in a large cohort of patients treated for locally advanced cervical cancer.

2. Patients and methods

2.1. Patients

From June 1992 until January 2013 all patients treated with primary radiotherapy with curative intent for cervical cancer at the Academic Medical Center were included in this retrospective mono-center cohort study. Inclusion criteria were newly diagnosed and histologically proven cervical cancer International Federation of Gynecology and Obstetrics (FIGO) stage IB to IVA. Patients with stage IVB were included if distant metastases were limited to the para-aortic lymph nodes below the renal veins.

All patients were treated with a combination of pelvic external beam radiotherapy (EBRT) and intracavitary brachytherapy. Para-aortic field radiotherapy was given in case of enlarged lymph nodes at the common iliac or para-aortic lymph node regions. In addition, in case of pathological lymph nodes, an external sequential boost to a total dose of 60 Gy was given. In case of parametrial involvement, an external parametrial boost (with a midline block) to a total dose of 60 Gy was given. In case of vaginal involvement of the lower (distal) third, the groins were also electively irradiated. The most frequently prescribed EBRT dose was 46 Gy in 23 fractions of 2 Gy. In our center, concurrent chemoradiation was introduced in 1999 and consisted of weekly cisplatin 40 mg/m^2. Deep hyperthermia was given as an alternative for chemotherapy in FIGO stages IIB2 to IVA [22].

All patients that were lost to follow-up within the first three months after the end of treatment were excluded. Standard follow-up after primary radiotherapy consisted of history taking and physical examination alternating between a radiation oncologist and a gynecologist for every three months for the first two years after treatment, and twice a year in the third to fifth year after treatment (or more frequently when indicated).

2.2. Methods

Data were retrospectively extracted from medical records in January and February 2016. Incidence, grade and date of first presentation of SLBT were retrieved from the patient's records. Treatment details were retrieved from an electronic database. Toxicity was scored according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0) [23] (Supplementary Table S1). Severe toxicity was defined as grade 3 or higher in the CTCAEv3.0. Severe acute bowel toxicity was defined as hospitalization for bowel toxicity occurring during treatment or within the first three months after treatment. Late toxicity was defined as symptoms occurring three months or later after treatment. The following items were scored: diarrhea, proctitis, gastrointestinal bleeding, fistula, and stenosis.

Patient records were also screened for potential risk factors that were selected a priori based on a literature search. Body mass index was analyzed both as a continuous and a dichotomous variable; patients with normal- or underweight (BMI <25) were compared to patients with overweight or obesity (BMI ≥25) according to WHO established categories. Alcohol and tobacco consumption were based on current consumption as described during the first consultation with the radiotherapist. Major abdominal surgery included all surgery at risk for developing intra-abdominal adhesions (Supplementary Appendix S1).

Finally, SES was also scored. This was based on status scores as provided by the Netherlands Institute for Social Research [24]. These status scores are provided per neighborhood as identified by their 4 digit zip code. Scores are constructed through a factor analysis based on four socio-economic characteristics: 1) the average income, 2) the percentage of persons with a low income, 3) the percentage of persons with a low level of education, 4) and the unemployment rate. The mean status score of the Netherlands was chosen as the cut-off value between high and low SES.

2.3. Statistical analyses

Analysis was performed using the highest toxicity grade recorded during follow-up per patient. A complete-case analysis was conducted, using pairwise deletion of cases with missing values for the univariable and listwise deletion for the multivariable Cox regression method. Records for SLBT were censored if these symptoms occurred simultaneously or after local, regional or metastatic recurrence of disease considering the uncertain distinction between symptoms of toxicity and recurrence. Patients who did not develop SLBT at the end of follow-up were censored on the date of last follow-up.

Univariable and multivariable analyses were performed using the Cox proportional hazards regression model. Multivariable analysis was performed using the backward conditional method for variables below the arbitrary p-value of 0.10 in univariable analysis. Several additional variables were selected for multivariable analysis based on an association found in literature, i.e. age, hypertension, diabetes mellitus, EBRT field, EBRT technique, and chemotherapy [25]. The proportional hazards assumption was evaluated graphically by assessment of the log-minus-log plots of hazard function. Variable elimination was assessed both by the Wald statistics and the Log likelihood ratio.

Socioeconomic status was analyzed as a surrogate for other risks, such as lifestyle factors. The relationship between socioeconomic status and other significant risk factors for severe late bowel toxicity related to lifestyle were assessed by cross tabulation. The relative risk of BMI on SLBT was illustrated graphically with a spline model. Actuarial survival and time-to-event were analyzed by the Kaplan-Meier method and log-rank test.