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**CLINICAL INVESTIGATION** **Cervix**

# INTESTINAL MALABSORPTION IN LONG-TERM SURVIVORS OF CERVICAL CANCER TREATED WITH RADIOTHERAPY

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**Purpose:** **The aim of this cross-sectional study is to investigate the associations between pelvic radiotherapy (RT) and markers of intestinal absorption in cervical cancer survivors (CCSs). We compared patient data with normative data from a reference population and explored the associations between cobalamin status and clinically significant diarrhea and depression.**

**Methods and Materials:** **Fifty-five CCSs treated with RT in 1994–1999 were included in 2005 in a follow-up questionnaire study exploring physical and psychological symptoms. Blood tests, including serum (S)-vitamin $B_{12}$, S-methylmalonic acid, S-folate, erythrocyte-folate, and plasma homocysteine, were analyzed. Differences in median values between CCSs and reference populations were evaluated by using Wilcoxon tests. Associations between variables were examined by means of multiple regression analyses.**

**Results:** **Median S-vitamin $B_{12}$ level was significantly lower and median S-methylmalonic acid level was significantly higher in CCSs compared with the reference population ($p < 0.001$). Correction for renal function verified a likely cobalamin deficiency in 20% of CCSs (11 of 55). Diarrhea or depression was not significantly related to any of the mentioned markers of cobalamin or folate status. Fifteen percent of CCSs (8 of 55) had subnormal S-calcium values.**

**Conclusions:** **Significant cobalamin deficiency was observed in 11 (20%) and low calcium level was observed in 8 CCSs (15%) 6–12 years after pelvic RT. Neither diarrhea nor depression was associated with this deficiency. Routine monitoring of S-vitamin $B_{12}$ level is recommended, and regular intake of cobalamin should be considered in CCSs treated with RT.** © 2009 Elsevier Inc.

**Cervical cancer, Radiotherapy, Long-term survivors, Malabsorption, Cobalamin deficiency.**

## INTRODUCTION

Radiotherapy (RT) of the pelvis may cause irreversible injury to the intestines, characterized by submucosal lesions with inflammation, atrophy, and fibrosis. Radiation-induced fibrosis can lead to such gastrointestinal complications as strictures, mucosal ulceration, and necrosis with bleeding, perforation, and/or fistulas (1, 2). Although radiation injuries of the bowel most frequently occur in the rectosigmoid part of the colon, the terminal ileum also may be susceptible to damage because the position of the ileocecal valve is fixed, and this part of the intestines is located within the radiation field (3, 4).

Postirradiation symptoms, such as diarrhea and steatorrhea, may be associated with malabsorption, bacterial overgrowth, and rapid intestinal transit time (5, 6). There is limited knowledge about intestinal absorption of biochemical markers (*e.g.,* blood levels of minerals, proteins, and vitamins) in cervical cancer survivors (CCSs) after RT. Some studies investigated vitamin $B_{12}$ (cobalamin) deficiency in CCSs and reported a prevalence of 12–15% (7–11). However, the majority of these studies were performed within 2 years after RT, and they regularly included heterogeneous samples of patients with gynecologic cancer. Only one study from 1984 included a homogeneous sample of long-term

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CCSs (9). All these studies used serum (S) vitamin $B_{12}$ level to evaluate cobalamin status. However, use of this marker alone results in low sensitivity and specificity of cobalamin deficiency. Supplementary measurements of the two metabolites that accumulate when S-vitamin $B_{12}$ is lacking, namely, S-methylmalonic acid (S-MMA) and plasma (P) homocysteine (P-Hcy), have shown much better diagnostic accuracy concerning cobalamin deficiency (12, 13). However, automatic assumption that isolated increased S-MMA and P-Hcy levels indicate cobalamin deficiency must be avoided because levels of these markers can increase when glomerular filtration rate is decreased (6, 14). The P-Hcy level also increases with age, in the case of folate deficiency, in smokers, and in patients with overt hypothyroidism (15–17).

Detection of cobalamin deficiency is important because even a moderately decreased S-vitamin $B_{12}$ level may be associated with hematologic, neurologic, and cognitive symptoms, such as depression or cognitive impairment (18, 19). In the elderly, cobalamin deficiency is assumed to be involved in the development and progression of dementia (19), particularly if there is a concomitant folic acid deficiency.

The first aim of this study is to investigate the effect of pelvic RT on cobalamin status and other nutritional markers of intestinal absorption in CCSs compared with reference populations. Second, we want to study the interrelationship between biochemical variables relevant to cobalamin deficiency. Third, we want to explore associations between biochemical markers of cobalamin deficiency and relevant clinical variables.

## METHODS AND MATERIALS

### *Patients and treatment*

In 1994–1999, nearly all patients with locally advanced cervical cancer (International Federation of Gynecology and Obstetrics Stages Ib2–IVa) who were treated with curative intention at the Norwegian Radium Hospital (Oslo, Norway) were included in the Nordic Cervical Cancer Study and offered standardized RT. None of the included patients had serious gastrointestinal diseases, such as ulcerous colitis or Crohn's disease, at baseline. Patients received external beam RT and intracavitary RT using standardized regimens. No patient underwent chemotherapy.

The clinical target volume received 45 Gy in 25 fractions/day through the anterior-posterior/posterior-anterior fields. The gross tumor volume received an additional 5-Gy tumor boost in patients with tumors 8 cm or less in diameter (Type 1 regimen) and 15-Gy tumor boost in patients with tumors greater than 8 cm in diameter (Type 2 regimen). The maximal planned treatment time was 6 weeks in the Type 1 regimen and 7 weeks in the Type 2 regimen. Patients with enlarged para-aortic lymph nodes received an extended field of irradiation (50.4 Gy/28) to tumor and lymph nodes with a four-field technique. Intracavitary RT was interposed during the external course, with a standard prescribed dose to Point A of 4.2 Gy/fraction. Additional details about the treatment are described elsewhere (20).

Of 381 patients included in the Nordic Cervical Cancer Study at the Norwegian Radium Hospital, 147 were still alive on Jan 1, 2005. These patients received a mailed questionnaire including the Late Effects Normal Tissues–Subjective, Objective, Management, Analytic (LENT-SOMA) (21) and the Hospital Anxiety and Depression Scale (HADS) (22) to be filled in and returned with a written consent. Of 91 CCSs (62%) who returned the questionnaire, 57 (66%) underwent a blood test at their general practitioner's office (Fig. 1).

### *Reference population*

A study-specified control group is lacking. To compensate for this, we used available reference values, if necessary, age-adjusted and gender-specific ones, from the healthy population that contributed to the Nordic Reference Interval Project (23, 24) and in-house reference populations. The Nordic Reference Interval Project reference individuals were aged 18–91 years and recruited from the general population. Of the total sample ($N = 3{,}002$), 96% were of Nordic origin, 28% were aged 51–70 years, and 15% were older than 70 years. They had a median body mass index (BMI) of 23.7 kg/m$^2$, 10% smoked more than five cigarettes/day, and 4% had a chronic disease. In-house reference groups from the Department of Medical Biochemistry, Rikshospitalet University Hospital, were used for P-ferritin ($N = 108$ women; median age, 39 years; range, 19–64 years), P-Hcy ($N = 95$ women; median age, 48 years; range, 24–72 years), S-vitamin $B_{12}$ ($N = 198$; both genders; median age, 48 years; range, 18–72 years), S-folate ($N = 118$; both genders; median age, 38 years; range, 18–65 years), and S-MMA ($N = 74$; both genders; median age, 51 years; range, 37–69 years).

### *Laboratory measurements*

Fasting blood samples obtained by the general practitioners were transported to the laboratory at Rikshospitalet University Hospital, where they were stored at −20°C until analyses were performed. The different biochemical markers and analytic methods used are listed in Table 1. All laboratory methods, except for S-vitamin 25-OH $D_3$ and S-MMA, were accredited to the International Organization for Standardization/International Electrotechnical Commission

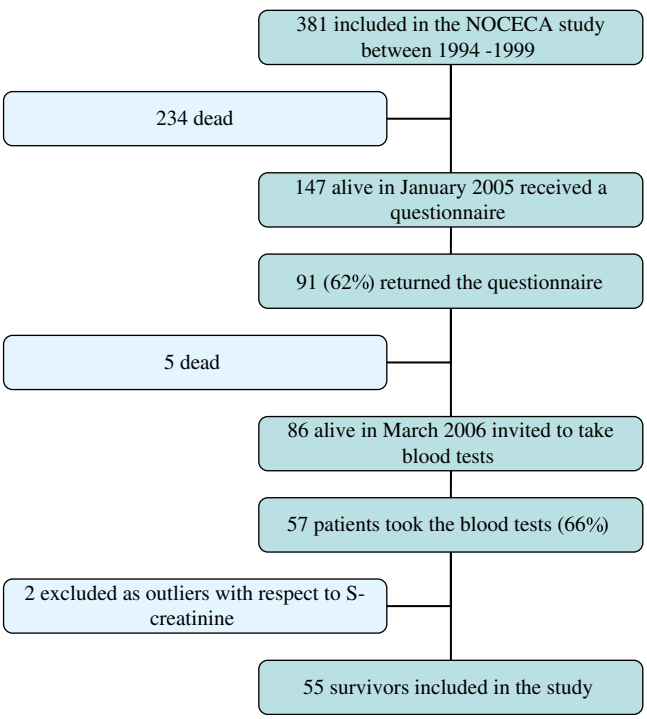


Fig. 1. Flow chart of patients included in the present study. NOCECA = Nordic Cervical Cancer; S = serum.