# Rectal carcinoma after radiotherapy for cervical carcinoma in patients with a family history of colorectal carcinoma: report of two cases

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**Summary**

Rectal carcinoma is a rare, but well documented late complication of pelvic irradiation. Little is known about the factors predisposing to the development of radiation-associated rectal carcinoma. We present two patients who developed rectal carcinoma 17 and 26 years after radiotherapy for carcinoma of the uterine cervix. In one patient, mutation in exon 4 of the hMLH1 gene was detected. Radiation-associated rectal carcinoma represents a rare late toxicity of radiotherapy for cervical carcinoma that may occur in patients with a family history of colorectal carcinoma, including hereditary non-polyposis colorectal cancer.

*Key words:* Cervical carcinoma; Hereditary non-polyposis colorectal cancer; Radiotherapy; Rectal carcinoma.

## Introduction

Radiotherapy alone or in combination with concomitant systemic administration of chemotherapy is an effective therapeutic modality in patients with carcinoma of the uterine cervix, and chemoradiotherapy currently represents the standard of care in patients with advanced cervical carcinoma. Rectal carcinoma is a rare, but well documented late complication of pelvic irradiation. Most cases described so far have been reported in patients treated with radiotherapy for cervical carcinoma [1-4], although cases of radiation-induced rectal carcinoma have also been documented in patients treated for other tumors. In patients with cervical carcinoma treated with radiotherapy, the risk of rectal carcinoma is significantly increased compared to the general population or patients treated with surgery alone, but the absolute number of cases is relatively small [1-4]. For example, among 6,665 patients with cervical carcinoma treated with radiotherapy, 25 cases of rectal carcinoma were observed while 13 cases were expected [1]. Little is currently known about the factors predisposing individual patients to the development of radiation-associated rectal carcinoma.

Most cases of colorectal carcinoma are sporadic tumors caused by somatic mutations. Although a family history of colorectal carcinoma is associated with increased risk for this tumor, most tumors in patients with a positive family history seem to have non-hereditary etiology and are probably caused by other factors, e.g., diet, lifestyle or environment. Only 1-3% of cases of colorectal carcinoma are thought to be hereditary [5]. Prominent among the hereditary syndromes of colorectal carcinoma is hereditary non-polyposis colorectal cancer (HNPCC; Lynch syndrome). HNPCC is inherited in an autosomal-dominant manner and is caused by mutations in DNA mismatch repair genes (hMSH2 or hMLH1). These mutations do not cause malignant transformation directly, but result in a so-called replication error phenotype that leads to accumulation of mutations in other growth-regulatory genes [5].

In the present report we describe two patients who had rectal carcinoma 17 and 26 years after pelvic irradiation for carcinoma of the uterine cervix. Both patients had a positive family history for colorectal carcinoma, and in one patient HNPCC was subsequently diagnosed.

## Case Reports

*Case 1*

A 62-year-old woman presented in October 1999 with rectal carcinoma. Her personal history was remarkable for cervical carcinoma treated by pelvic irradiation at the age of 36, and carcinoma of the cecum treated by right hemicolectomy at the age of 54. The patient's mother died at the age of 58 of advanced abdominal cancer of uncertain primary, her sister died at the age of 56 of gastric carcinoma, and her brother was diagnosed at the age of 54 with colon carcinoma. Her maternal uncle died at the age of 60 of gastrointestinal carcinoma and her maternal grandmother died at the age of 42 of gastric carcinoma. The cervical carcinoma (Stage IIb) manifested after prior supravaginal hysterectomy for myoma. Histologic examination revealed poorly differentiated carcinoma. The patient was treated by radical radiotherapy (pelvic irradiation using $^{60}$Co 49.4 Gy five times weekly in fractions of 1.9 Gy and brachytherapy using a uterovaginal applicator at the dose of 40 mg radium for 72 hours). Anteroposterior/posteroanterior fields were used and, after reaching the dose of 26,6 Gy, midline shielding was added.

In October 1999 the patient presented with hematochesia of about 12 months' duration. Coloscopy revealed a polyp 4 cm in

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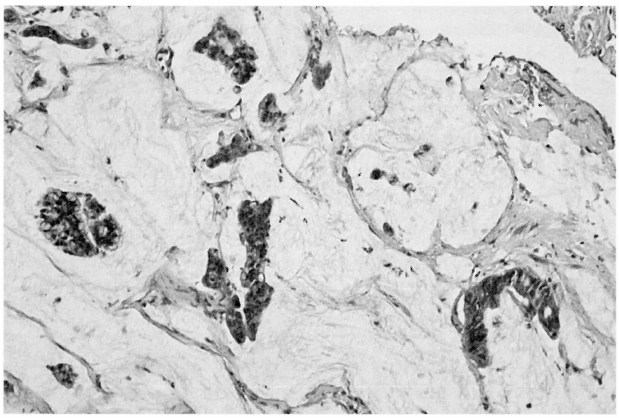

Figure 1. — Histological appearance of rectal carcinoma in patient 1
Shown is a section of moderately differentiated adenocarcinoma of intestinal type showing focally marked mucinous features (hematoxylin and eosin stain, original magnification x 100).

diameter, and on histological examination moderately differentiated adenocarcinoma was diagnosed. Clinical staging based on endosonography was T3N0M0 (Stage II). Because of earlier pelvic radiotherapy, only a brief course of preoperative brachytherapy was administered, and on November 11, 1999 the patient underwent abdominoperineal resection. Histological examination revealed Stage I (pT2N0M0) rectal carcinoma with marked mucinous differentiation (Figure 1). Because of the stage no adjuvant therapy was indicated.

Since January 2000, the patient complained about weakness, difficult swallowing, speech difficulty, ptosis and diplopia. A diagnosis of myasthenia gravis was made and thymoma was diagnosed on computed tomography (CT). On March 2, 2001 the patient underwent thymectomy. Microscopic examination revealed benign thymoma. In October 2001 the patient complained about discomfort in the hypogastrium. CT scan revealed a large 7 cm presacral mass in continuity with a tumor in the vicinity of the common iliac veins, and multiple ulcerating lesions were evident on vaginal mucosa on physical examination. There was no evidence of liver or lung metastases. Examination of biopsy samples of vaginal lesions revealed malignant cells. Because of recurrent rectal carcinoma, treatment with a combination of irinotecan, leucovorin, bolus and infusional 5-fluorouracil (Douillard regimen) was started. Stable disease was first detected on control CT scans, but the disease progressed in June 2002. Because of poor performance status the patient was afterwards treated only symptomatically and died in September 2002.

Screening examination of hMSH2 and hMLH1 genes revealed that the patient and her brother were heterozygous for the mutation c.350C>T (p.Thr117Met) in exon 4 of the hMLH1 gene.

*Case 2*

A 61-year-old female presented in September 1998 with rectal carcinoma. The personal history was remarkable for Stage II cervical carcinoma treated by radical radiotherapy ($^{60}$Co 50 Gy and 2 x 65 mg radium for 48 hours) 17 years before. Both of her brothers died around the age of 50 of colorectal carcinoma, but her parents lived into their 80s without apparent malignancy.

The patient underwent abdominoperineal resection on October 9, 1998, and examination of the resection specimen revealed moderately differentiated adenocarcinoma 2 cm from the anal verge (pT3N0M0). Increased mucus production was noted. The patient was subsequently treated by 12 cycles of adjuvant leucovorin, bolus and infusional 5-fluorouracil (de Gramont) regimen. At the last control in June 2006 the patient was without recurrence.

Screening examination of hMSH2 and hMLH1 genes did not reveal any mutations.

## Discussion

We report here two patients with a family history of colorectal carcinoma who were treated with pelvic irradiation for cervical carcinoma and developed rectal carcinoma two decades later. Both cases fulfill the criteria for radiation-associated tumor [6] as the tumors arose in a previous radiation field, the secondary malignancy differed histologically from the irradiated primary, the latency period was more than six years, and statistical data showed increased risk of rectal carcinoma following pelvic radiotherapy [1-4]. In one patient, who also met the Amsterdam II criteria [5], a mutation diagnostic of HNPCC was detected while no mutation in DNA mismatch repair genes was detected in the other patient, who only had two siblings affected with the disease. To the best of our knowledge, the present case is the first description of radiation-associated rectal carcinoma in a patient with HNPCC. Radiation-associated rectal carcinoma has been described after radiotherapy for different tumors, including bladder carcinoma, endometrial carcinoma, lymphoma or prostate carcinoma, but most cases have been described in patients with cervical carcinoma. This may be explained by the relatively high incidence of cervical carcinoma in younger women with long life expectancy in the case of cure, effectiveness of radiation therapy in tumor control and its widespread use over the last decades. Other common gynecological neoplasms, endometrial carcinoma and ovarian carcinoma, are associated with increased risk of second-primary colorectal carcinoma, but no such increased risk has been described for cervical carcinoma. Endometrial carcinoma and, to a lesser extent, ovarian carcinoma, are common in HNPCC (Lynch II) syndrome, but cervical carcinoma is not a part of the presentation in this hereditary cancer syndrome. In patients with radiation-associated rectal carcinoma after radiotherapy for cervical carcinoma an unusually high proportion of patients with mucin-producing carcinomas has been reported [7]. Mucinous differentiation was also observed in both patients presented here, and this histological feature may represent a characteristic of radiation-induced rectal carcinoma. The mutation in exon 4 of the hMLH1 gene found in case 1 (c.350C > T (p.Thr117Met)) has been repeatedly detected in patients with HNPCC, and its pathogenicity has been confirmed by functional analysis [8].

Little is known about the factors predisposing individual patients for the development of radiation-associated rectal carcinoma after therapy for cervical carcinoma.

The radiation dose is certainly an important factor determining the risk of radiation-associated rectal carcinoma. The risk of rectal carcinoma also seems to increase with time [1-4]. Estimates of risk (risk ratio) reported in the literature range between 2 and 5. Because of the rarity of this complication and retrospective nature of all large series, it was not possible to identify other factors determining the risk of radiation-associated rectal carcinoma after pelvic radiotherapy. Although HNPCC is not associated with an increased incidence of cervical carcinoma, individuals with HNPCC may be, because of the nature of the defect in DNA mismatch repair, more susceptible to radiation-induced carcinogenesis. In an experimental study, no increase in chromosomal aberrations, but a higher rate of chromatid exchanges was observed after irradiation in lymphoblasts from HNPCC patients compared to control cell lines [9]. In one analysis of patients with radiation-associated rectal carcinoma published so far, microsatellite instability, an indicator of replication error phenotype that is characteristic of HNPCC, was not detected in any of five patients studied [10]. Asymptomatic individuals with HNPCC are currently being identified with increasing frequency through genetic counseling and testing. Incidence of radiation-associated tumors should be monitored in these patients, although given the low incidence, low use of radiotherapy in many tumors associated with HNPCC and long interval prior to the manifestation of radiation-associated cancer, it may take several decades before an increase in the incidence of radiation-associated tumors in HNPCC patients. In the meanwhile only anecdotal reports like the present case could indicate increased risk of second primary radiation-associated rectal carcinoma in this patient population. Vigilance may be warranted in the follow-up of patients with HNPCC treated with pelvic radiotherapy. Testing for HNPCC should also be offered to patients with radiation-associated rectal carcinoma and a family history of neoplasms associated with HNPCC.

In conclusion, radiation-associated rectal carcinoma represents a rare late toxicity of radiotherapy for cervical carcinoma that may occur in patients with a family history of colorectal carcinoma, including HNPCC.

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