

Case Analysis

Radiation-Induced Cancers of the Colon and Rectum-Analysis of Five Cases

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Key Words

Radiation;

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Purpose. Acute radiation injury may cause serious complications to the pelvic colon and rectum especially in patients with pelvic malignancies. There are considerable differences of opinion about the risk for the development of colorectal cancer following pelvic irradiation. We present five patients whose tumors were considered to be radiation-induced.

Methods. A retrospective review of medical records was performed to identify colorectal cancer patients who had previously received radiotherapy following surgical treatment for their primary cancers.

Results. Review of medical records revealed 5 patients (one male and four female). Their age ranged from 65 to 87 years, with an average of 73.4 years. Four patients had rectal cancer and one patient had sigmoid colon cancer. All of these patients had radiation therapy at least 10 years prior to the development of colorectal cancer. Three patients had received radiation therapy for cervical cancer, one for bladder cancer, and one for rectal cancer. One patient underwent low anterior resection, one abdominoperineal resection and three Hartmann's resections of the colorectal cancers.

Conclusion. Irradiation may play a role in the development of colorectal cancer. Benefit of radiotherapy should be evaluated against the risk of development of cancer in the radiated bowel.

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Radiation is frequently offered to the patients with pelvic malignancies as primary or adjuvant therapy. Radiation injury may cause serious complications to pelvic organs such as the colon and rectum. There are considerable differences of opinion about the risk for the development of colorectal cancer following pelvic irradiation, and those who have received pelvic irradiation are presumed to be at a higher risk for colorectal cancer. Much of the evidence that supports radiation as a cause of colorectal cancer comes from case reports.¹⁻⁵

Black and Ackerman demonstrated the criteria⁶

for classifying a tumor as radiation-induced as following: (1) an adequate time, probably 10 years or more, should exist between completion of radiotherapy and the diagnosis of carcinoma; (2) radiation exposure should be great and that "severe" radiation damage to tissue adjacent to the cancer should be demonstrable. Slaughter and Southwick reported nine patients who developed carcinomas in a field of radiation therapy.⁷ Even if all criteria are met, it is still possible that a tumor in an irradiated area is an incidental occurrence, since most therapeutic radiation is directed at the area in which most colorectal cancer naturally occur.

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We hereby analyzed five patients who met the criteria of radiation-induced colorectal cancer.

Cases Analysis

From 1986 to 2004, five patients who had radiotherapy at least 10 years prior to the development of colorectal cancer were identified. They met the criteria suggested by Black and Ackerman, and were believed to have colorectal cancer caused by radiation injury. One patient was male and four were female. Their age ranged from 65 to 87 years old, with an average of 73.4 years. Four patients had rectal cancers and one patient had sigmoid colon cancer. Three patients had previously received radiation therapy for cervical cancers and one each for bladder cancer and rectal cancer. (Table 1)

Case one is a 65-year-old female with rectal cancer who underwent low anterior resection 21 years ago. She was given post-operative radiation therapy. The total dose was 6000 cGy, and radiotherapy was completed within 51 days. No cancer recurrence or distant metastasis was found during regular follow up. Eighteen years after radiation therapy, she presented with rectal bleeding and body weight loss. Sigmoidoscopy revealed a tumor mass with slightly elevated margin and central ulceration in the low rectum, about 4 cm from the anal verge. Friable rectal mucosa was also seen in the rectum, suspecting proctitis. Pathologic report was adenocarcinoma (the tumor grew in cribriform or complex glandular pattern set in a fibrous stroma). She subsequently underwent abdominoperineal resection of the rectal cancer and is still alive without evidence of recurrent cancer.

Case two is a 80-year-old female with cervical cancer who received abdominal total hysterectomy and bilateral salpingo-oophorectomy more than 20 years ago. She was given post-operative radiation therapy. A total dose of 6000 cGy, was given in a span of 33 days. No cancer recurrence or distant metastasis was found during regular follow up. Twelve years after radiation therapy, she presented with bloody stool and tenesmus. Colonoscopy revealed severe inflammation, edematous mucosa with narrowing of rectum, about 10 cm from the anal verge. Friable tissue was

noted, and radiation proctitis was suspected. Pathologic report was moderately differentiated adenocarcinoma. She underwent low anterior resection of rectal cancer and is still alive 20 years following surgery.

Case three is a 65-year-old male with bladder cancer who received total cystectomy with ileal conduit 15 years ago. He was given post-operative radiation therapy. The total dose was 8100 cGy, and radiotherapy completed within 90 days. No cancer recurrence or distant metastasis was found during regular follow up. He presented with low abdominal pain and bloody stool 10 years after radiation therapy. Sigmoidoscopy revealed a big ulcer with some exudate in the sigmoid colon and suspected radiation proctitis. Biopsy revealed poorly differentiated adenocarcinoma. He underwent Hartmann's resection and is alive with metastatic disease.

Case four is a 70-year-old female with cervical cancer who received operation and a full course of radiation therapy 20 years ago at another hospital. Therefore, the radiation data were not available. Sixteen years after radiation therapy, she presented with chronic diarrhea off and on with stool coming from vagina. Colonoscopy revealed sigmoid colon stricture and suspected radiation proctitis. A rectal-vaginal fistula was also noted. An indurated mass at the rectosigmoid colon with severe adhesion to the urinary bladder was noted during operation. Pathology revealed adenocarcinoma of rectum. She underwent Hartmann's resection and died of metastatic disease.

Case five is a 87-year-old female with cervical cancer who received operation and a full course of radiation therapy 30 years ago at another hospital. Twenty-five years after radiation therapy, she pre-

Table 1. Characteristic of the patients

Study period	1986-2004
Post radiation	10~25 years
Total number of patients	5
M:F	1:4
Age	65-87 y/o (Ave. 73.4 y/o)
Rectal: Colon	4 : 1
Previous cancer for radiotherapy	
Cervix	3
Urinary bladder	1
Rectum	1

sented with body weight loss and low abdominal pain. Bright-red stool was also noted. Endoscopy revealed the middle rectal stricture with easy contact bleeding. Radiation proctitis was suspected and biopsy was performed. The pathologic report showed coagulative necrotic tissue with some inflammatory cells and early tissue reaction. There was no evidence of viable squamous cell carcinoma tissue. Double contrast barium enema revealed persistent rigid narrowing of the rectum, highly suggestive of rectal carcinoma. Due to persisting low abdominal pain, so she underwent

Hartmann's resection of the rectal lesion. The pathologic report revealed poorly differentiated adenocarcinoma, Dukes' B lesion. She died of post-operative acute respiratory distress syndrome. (Table 2 and 3)

Discussion

Investigation of Japanese populations in Hiroshima and Nagasaki following the atomic bombs found a significantly elevated mortality rate from co-

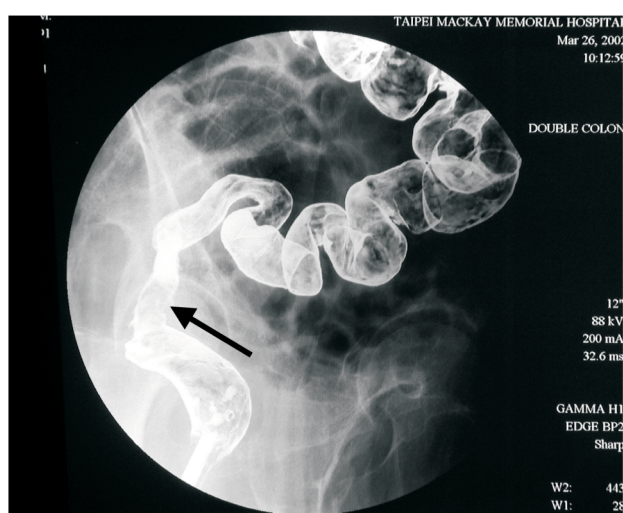


Fig. 1. Double contrast barium enema revealed constant rigid narrowing and ulceration of the rectum (arrow), suggesting radiation proctitis but not tissue proven pre-operatively.

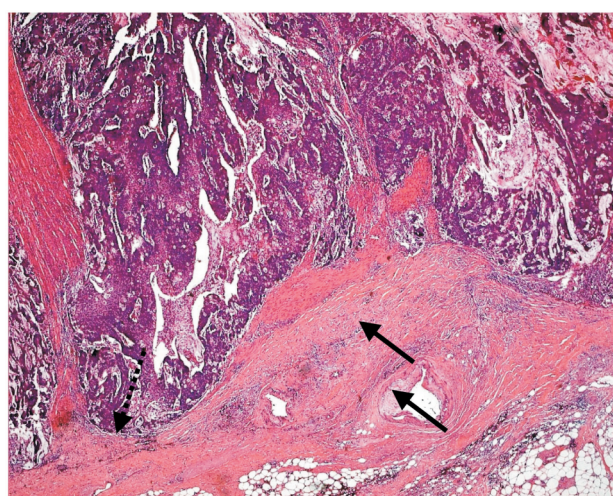


Fig. 2. The pathologic picture revealed adenocarcinoma invaded through the muscle layer (dotted arrow). Perirectal tissue and the intima of vessel showed fibrotic change (arrow), this change related with radiation therapy.

Table 2. Surgical procedures and outcome

Operative method	Case number	Outcome
Low anterior resection	1	Alive 20 years following surgery
Abdominoperineal resection	1	Alive without evidence of disease
Hartmann's resection	3	One patient was alive with metastatic disease; one patient died of ARDS postoperatively; one patient died of metastatic disease

Table 3. Radiation therapy data of the patient

	Radiation dosage (cGy)	Radiation interval (days)	Radiation proctitis	Time of secondary colorectal cancer after R/T (years)
Case 1	6000	51	Present	21
Case 2	6000	33	Present	20
Case 3	8100	90	Present	10
Case 4*	Not available	Not available	Present	16
Case 5*	Not available	Not available	Present	25

* Case 4 and 5 received radiation therapy at another hospitals.

lon cancer but not from rectal cancer.⁸ The result pointed out that irradiation was considered as a carcinogen, but this was still controversial. A study of women employed as radium dial painters showed increased risk for colon cancer. However, colorectal cancer was not demonstrated to be increased in radiologists, workers at a nuclear research facility and World War II radiology technicians. Radiation has been considered and placed in the category of a carcinogen by the Food and Drug Administration since 2005.

Many studies had discussed the relationship between the radiation therapy and colorectal cancer.⁹ Sandler et al reported the risk of radiation-induced colorectal cancers.¹⁰ They considered that women who were irradiated for gynecologic cancer might have a relative risk for subsequent colorectal cancer of 2.0-3.6 based on best estimates. The risk was calculated independently of any risk imposed by underlying disease. These women were appropriate targets for careful surveillance for colorectal cancer. Palmar et al.¹¹ presented a significantly elevated risk of rectal cancer following radiation for benign uterine bleeding. Liauw et al. reviewed 125 patients after radiation therapy for prostate cancer and revealed that there may be an increased but small risk of developing a second malignancy.¹² Birgisson et al.¹³ analyzed the occurrence of second cancers in patients with rectal cancer treated with external radiotherapy in addition to surgery. An increased risk of second cancers was found in patients treated with radiotherapy in addition to surgery for a rectal cancer, which was mainly explained by an increase in the risk of second cancers in organs within or adjacent to the irradiated volume.

The radiation injury pathway or pathogenesis of carcinogenesis is still controversial today. Dasu et al.¹⁴ demonstrated that dose inhomogeneity plays an important role in predicting the risk for secondary cancer, and therefore for predictive purposes it must be taken into account through the use of the dose volume histograms. They also suggest that the competition between cell killing and the induction of carcinogenic mutations has to be taken into consideration for more realistic risk estimations. Tsuji and colleagues performed genetic analysis of radiation-associated rectal cancer.¹⁵ The results suggested that the radia-

tion-associated rectal carcinomas examined in their study did not develop through the mutator phenotype pathway; rather, tumorigenesis was probably mediated through the multistep carcinogenesis pathway. Therefore, more studies on the radiation injury pathway are required.

Three of our cases had history of cervical cancer and received radiation therapy previously. Castro analyzed twenty-six patients with carcinoma of large bowel who were irradiated for carcinoma of cervix and uterus from 1926 to 1969.¹⁶ The majority of the cases met the criteria, thus suggesting a causal link. Most of the patients (69%) had patients had a postirradiation interval of over 10 years. Half of the patients had symptomatic radiation proctocolitis; 58% had histologic proof of radiation-related alterations which involved the bowel segment. Colloid carcinoma comprised 58% of the tumors, more than 10% in a general case series. Palmer and Spratt observed 471 irradiated cervical cancer patients who survived at least 10 years. There were two rectal cancer cases, higher than the 1.4 cases of expected.¹¹ Brack and Dickson identified 923 patients who survived over 5 years after radium treatment for cervical cancer. Twelve deaths from cancer of the rectum were observed,¹⁷ higher than the 4.35 cases of expected.

The relationship between radiation dosage and the incidence of secondary cancers is still controversial in present. Jao et al reviewed 76 cases of colon or anorectal cancer after pelvic irradiation for other malignant or benign lesions.¹⁸ The cancer developed at a mean of 15.2 years after irradiation, with peak frequency between five and ten years; 85 percent of the patients had a mild to prominent radiation reaction around the cancer. Among the 72 adenocarcinomas, 26 percent of the cancers were mucinous type. Only 17 percent of the patients presented with symptoms of radiation proctitis, and the mean radiation dosages were not high. High radiation dosage and severe radiation damage may not be essential for radiation-associated colorectal cancer. The overall five-year survival rate was 48 percent. However, some authors had the opposite opinion. Kendle and colleagues investigated a putative increased risk of rectal cancer subsequent to prostatic radiotherapy.¹⁹ They were unable to demonstrate a significant increased incidence of rectal

cancer in men irradiated for prostatic cancer in all 33,831 patients studied.

To our knowledge, there have not been any studies on anastomotic leakage rate after radiation. In our series, all of these five patients received surgical resection. Only one patient had low anterior resection with anastomosis, three had Hartmann's resection and one had abdominoperineal resection. Further investigation about this topic should be carried out in the future.

Conclusion

Radiation has been considered and placed in the category of a carcinogen. It should be kept in mind that radiation therapy could be the cause of colorectal cancer. More studies are required for confirmation of the relationship between radiation therapy and colorectal cancer. Benefit of radiotherapy, especially postoperative radiotherapy, should be evaluated against the risk of development of cancer in the radiated bowel.

References

1. Tamai ON, Miyazato E, Isa H, Hiroyasu T, Shiraishi, S, Kusano M, Muto T, Y. Higashi, M. Radiation-associated rectal cancer: report of four cases. *Dig Surg*. 1999;16(3):238-43.
2. Narui KI, Hideyuki Fujii, Shoichi Nojiri, Kazunori Tatsumi, Kenji Yamagishi, Shigeru Saito, Shuji Kunisaki, Chikara Imada, Toshio Nozawa, Akinori Ohki, Shigeo Ota, Mitsuyoshi Ichikawa, Yasushi Shimada, Hiroshi. A case of radiation-induced rectal cancer. *Nippon Shokakibyō Gakkai Zasshi - Japanese Journal of Gastroenterology*. 2006;103(5):551-7.
3. Tsunoda AS, Kawamura M, Marumori M, Kusano T, M. Ohta, H. Colorectal cancer after pelvic irradiation: case reports. *Anticancer Research*. 1997;17(1B):729-32.
4. Morita HK, N. Tamura, Y. Development of flat adenoma and superficial rectal cancer after pelvic radiation. *Journal of Clinical Gastroenterology*. 1998;26(3):171-4.
5. Miholic JS, C. Moeschl, P. Surgical therapy of radiation-induced lesions of the colon and rectum. *American Journal of Surgery*. 1998;155(6):761-4.
6. Black WCRA, L V. Carcinoma of the large intestine as a late complication of pelvic radiotherapy. *Clin Radiol*. 1965;16:278-81.
7. Slaughter DPS, H W. Mucosal carcinomas as a result of irradiation. *A.M.A. Archives of Surgery*. 1957;74(3):420-9.
8. Nakatsuka HS, Yamamoto Y, Sekine T, Ezaki I, Tahara H, Takahashi E, Shimoyama M, Mochinaga T, N. Tomita, M. et al. Colorectal cancer incidence among atomic bomb survivors, 1950-80. *Journal of Radiation Research*. 1992;33(4):342-61.
9. Baxter NN TJ, Durham SB, Rothenberger DA, Virnig BA. Increased risk of rectal cancer after prostate radiation: a population-based study. *Gastroenterology*. 2005;128(4):819-24.
10. Sandler RSS, D P. Radiation-induced cancers of the colon and rectum: assessing the risk. *Gastroenterology*. 1983;84(1):51-7.
11. Palmer JPS, D W. Pelvic carcinoma following irradiation for benign gynecological diseases. *American Journal of Obstetrics & Gynecology*. 1956;72(3):497-505.
12. Liauw SL SJ, Morris CG, Blasko JC, Grimm PD. Second malignancies after prostate brachytherapy: incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up. 2006;66(3):669-73. Epub 2006 Aug 2.
13. Birgisson HP, Lars. Gunnarsson, Ulf. Glimelius, Bengt. Occurrence of second cancers in patients treated with radiotherapy for rectal cancer. *J Clin Oncol*. 2005;23(25):6126-31.
14. Dasu A T-DI, Olofsson J, Karlsson M. The use of risk estimation models for the induction of secondary cancers following radiotherapy. *Acta Oncol*. 2005;44(4):339-47.
15. Tsuji T ST, Nakagoe T, Hidaka S, Shibasaki S, Tanaka K, Nanashima A, Yamaguchi H, Yasutake T, Tagawa Y. Genetic analysis of radiation-associated rectal cancer. *Journal of Gastroenterology*. 2003;38(12):1185-8.
16. Castro EBR, P P. Quan, S H. Carcinoma of large intestine in patients irradiated for carcinoma of cervix and uterus. *Cancer*. 1973;31(1):45-52.
17. Brack CBD, R J. Haines, B W. Townsend, L. Cervical cancer; factors influencing prognosis in intraepithelial and clinical carcinoma of the cervix uteri. *Obstetrics & Gynecology*. 1956;8(6):728-35.
18. Jao SWB, R W Jr. Reiman, H M. Gunderson, L L. Ilstrup, D M. Colon and anorectal cancer after pelvic irradiation. *Diseases of the Colon & Rectum*. 1987;30(12):953-8.
19. Kendal WSE, Libni. Macrae, Robert. Malone, Shawn. Nicholas, Garth. Prostatic irradiation is not associated with any measurable increase in the risk of subsequent rectal cancer. *International Journal of Radiation Oncology, Biology, Physics*. 2006;65(3):661-8.

病例分析

放射線誘發大腸直腸癌 — 五病例分析

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目的 放射線治療可能會導致在骨盆腔內的結腸與直腸嚴重的傷害。對於接受骨盆腔放射線治療後會引起結腸直腸癌危險因素，有許多不同的意見。這篇研究分析認為是放射線治療後引起的結腸直腸癌。

方法 從 1986 年到 2004 年，有五個患者接受放射線治療後經過十年以上，後來發現有結腸直腸癌。

結果 在五個患者當中，有一個為男性，其餘為女性。年齡從 65 歲到 87 歲，平均年齡 73.4 歲。有四個患者是直腸癌，有一個是乙狀結腸癌。有三個患者接受放射線治療的原因是之前有子宮頸癌；一個患者是因為膀胱癌；一個是因為直腸癌。有一個患者後來接受了低位直腸切除手術；一個接受腹部會陰切除手術。三個患者因為次發的癌症接受哈特曼氏切除。

結論 我們對於放射線治療可能引起的大腸直腸癌是需要注意的。放射線治療可能帶來的好處，應該要再進一步的評估，是否會使受到放射線的腸道發展成癌症的危險。

關鍵詞 放射線、大腸直腸癌。