LATE RADIATION PROCTITIS - THE INCIDENCE AND CONTRIBUTING FACTORS IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CARCINOMA TREATED AT PRETORIA ACADEMIC HOSPITAL

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Abstract:

Purpose:

To determine the incidence of late radiation proctitis in patients treated with radical radiotherapy in Pretoria Academic Hospital during a period when hypofractionated radiotherapy and external boosts were being utilised for the treatment of advanced carcinoma of the cervix.

Possible contributing factors were also examined in an attempt to identify areas where possible changes to our treatment policies would ensure effective palliation without severe late radiation proctitis.

Materials and methods:

During the period January 1999 – December 2000, 62 patients with advanced carcinoma of the cervix underwent radical radiotherapy, employing hypofractionated protocols and external boosts. The patients' hospital files were reviewed retrospectively to determine the incidence of late radiation proctitis. X^2/Fischer's exact test for categorical variables was also employed in an attempt to identify possible contributing factors.

Results:

Incidence of late radiation proctitis was 46,77%. Of these patients, 12,5% required surgical intervention. There was a significantly increased incidence of late radiation proctitis in patients with stage IIIB carcinoma of the cervix (p=0,018). The higher dose per fraction, especially of the external boost (20Gy in 5 fractions) also contributed to the significantly increased incidence of late radiation proctitis.

Age and the prescription of blood transfusions during treatment did not seem to influence the incidence significantly. Due to incomplete data, no conclusion could be drawn on the incidence of late radiation proctitis and HIV status.

Conclusion:

Patients treated for advanced carcinoma of the cervix with hypofractionated radiotherapy and external boosts had a significantly high rate of late radiation proctitis. Due to the lack of brachytherapy facilities, this increased incidence was strongly influenced by the high dose per fraction of the external boost. Omission of brachytherapy in the radiotherapeutic management of locally advanced cervical cancer results in reduced local control and survival. This study therefore has important palliative implications in that the identification of a contributing factor to an unacceptably high incidence of late radiation injury supported a change in clinical practice at a time when brachytherapy facilities were not available in our department. Many of our patients are from rural areas where medical support is lacking, hence a high incidence of severe radiation proctitis as well as the symptoms of pelvic tumour persistence would be undesirable as this would lead to increased suffering.

Introduction

Carcinoma of the cervix is the most common cancer found in South African women, with the disease accounting for 16,47% of all cancers registered with the South African Cancer Registery[1]. More than 20 new cases are diagnosed per 100 000 of the total female population[2].

In South Africa approximately 75% of patients present with advanced stage disease. This is the exact opposite to the situation found in developed countries and leads to a poorer prognosis[2].

Patients with HIV infection have both a higher incidence of pre-malignant lesions or cervical cancer and a more rapid course[2]. The Centre of Disease Control [CDC] designated invasive cervical cancer as an AIDS case-defining illness in the 1993 Expanded Surveillance Cancer Definition of AIDS.

Locally advanced cancer of the uterine cervix is primarily treated with radiation therapy utilising a combination of external beam and intracavitary brachytherapy[3]. The overall survival of patients with stage IIB cervical cancer is about 60-65% while the survival of patients treated with stage IIIB cervical cancer is 40%[3].

The tolerance of the normal tissues within the pelvis limits the dose that can be given to the clinical target volume. The dose of radiation prescribed encompasses the volume of the primary cancer present as well as the regional nodes according to internationally accepted standards[4].

Local control for a clinically obvious tumour requires more than 60Gy[5].

The acute effects of radiotherapy can become obvious after 20- 30Gy. These effects are caused by ionising radiation on the epithelium of the intestine and bladder. Symptoms include diarrhoea, abdominal cramps, nausea, frequent urination, and occasionally bleeding from the bladder or bowel mucosa.

The late effects of radiotherapy result from the induction of vasculitis and fibrosis in late-reacting tissues, and occur several months to years after completion of radiotherapy. Late complications often cause significantly more morbidity than acute effects, which are self-limiting. Radiation-induced rectal complications are the most frequent sequelae after radiotherapy for cervical cancer. While the small bowel is more radio-sensitive than the rectum, the latter is more vulnerable due to its anatomical position[6].

Radiation-induced rectal complication is the main late sequelae after radiotherapy of cervical cancer. The small bowel is the most sensitive to radiation, but the rectum is more vulnerable owing to its fixed anatomy and position in relation to the cervix. Although late complications may increase with time, 75% of late complications develop within 30 months of radiotherapy[7].

Late complications of radical irradiation for cervical cancer occur in 5-15% of patients. The incidence of late complications depend on the specific tolerance of the normal tissues irradiated, the size of the daily dose per fraction, the total dose administered and the volume irradiated[8]. Every effort should be made to minimise the high-dose treatment volume while adequately encompassing the tumour and its regional lymph nodes.

Studies have also reported that the age of the patient and stage of disease also play a role in the development of radiation proctitis[9].

Serious bladder complications occur in approximately 7% of cases[11]. Rectal and recto-sigmoid complications occur in 6.4-8.1% of patients, and include bleeding, strictures and perforation.[12, 13]

Bleeding from proctosigmoiditis should be treated with a low-residue diet, anti-diarrhoeal medications, steroid enemas and sucralfate enemas. This could control bleeding in approximately 65% of cases[10]. Formalin application has also been shown to be effective in controlling chronic bleeding[26], with almost 100% control of persistent bleeding[27]. In extreme cases, a colostomy may be required to rest the bowel completely, and occasionally resection of the rectosigmoid must be performed.

Rectovaginal fistulas or rectal strictures occur in fewer than 2% of patients. Fistulas can be successfully closed with bulbocavernosus flaps[14]. Occasionally

resection with anastomosis is feasible. Patients presenting with severe and sustained rectal bleeding, after failure of enemas or formalin application to control symptoms, are usually candidates for a bypass colostomy. This is usually performed as a temporary measure lasting 3-9 months.

Radiation injury to the rectum has been the most common and distressing late complication of radiotherapy for cervical carcinoma. Prediction and prevention of this complication has become a central issue of radiation therapy for gynaecologic cancers. The identification of possible contributing factors to the incidence of rectal injury is paramount in patients where prognosis is poor or where long term control of the disease is questionable. This will prevent a patient suffering from both late radiation proctitis and progression of her disease.

Objective

The primary objective of this study is to determine the incidence of late radiation proctitis in patients with advanced stage cervical carcinoma receiving radiotherapy for curative intent at Pretoria Academic Hospital. Treatment during the period of study consisted of external Beam Radiation Therapy [EBRT] with a boost delivered by means of external radiotherapy (owing to a lack of brachytherapy equipment at our hospital during this period).

The secondary objective is to examine, by means of a retrospective cohort analysis, the following factors which could contribute to the occurrence of late radiation proctitis: age, stage of disease, HIV-status, total radiation dose, dose per fraction, and whether blood transfusions were received during treatment in the proctitis and non-proctitis groups.

Materials and Methods

We reviewed 62 patients who received radical radiotherapy from January 1999-December 2000 in Pretoria. All patients had International Federation of Gynaecology and Obstetrics stage IIb- IVa carcinoma of the cervix, and were evaluated in a retrospective cohort study.

Patients were initially evaluated by a general and pelvic examination, routine blood investigations, chest x-ray and abdominal- and pelvic ultrasound. The diagnosis was confirmed by means of a biopsy. If the pelvic ultrasound was suspicious for thickened bladder mucosa, a cystoscopy with biopsies was done. The age of the patient, her HIV-status, stage of disease, whether she received a blood transfusion or not, radiation dose and dose per fraction and development of late proctitis were recorded retrospectively from patient files.

External Beam Radiation Therapy [EBRT]

All patients were treated initially with EBRT. Whole-pelvic irradiation was given by was given by means of rotational fields on the Cobalt 60 machines. This allows for more patients to be treated as total treatment time is shorter and set-up is quicker. Before February 2000, the dose to the entire pelvis was 42Gy in 14 fractions in stage IIIB and IVA cervical cancer. Patients with stage IIB disease received 40Gy in 16 fractions to the entire pelvis.

All patients received an additional dose of 12Gy in 4 fractions to a shortened field encompassing the true pelvis. This volume was also given using the pendulum technique on the same Cobalt 60 machine the patient had received her whole-pelvic irradiation on. Thus the patients with stage III/IV treated with 42Gy in 14 fractions plus 12Gy in 4 fractions received an equivalent total dose of 65 Gy if using the ID2 tables to predict for late effects (a/b ratio =3). The ID2 is the total normalised tumour dose (NTD) or linear quadratic effective dose (LQED) for a 2 Gy fraction. For those patients with stage IIB treated with 40Gy in 16 fractions plus 12 Gy in 4 fractions, the ID2 for late effects was 58,4Gy.

After March 2000 the dose to the entire pelvis was changed to 40 Gy/ 16 fractions for patients with stage IIIB and IVA disease, the additional 12Gy in 4 fractions to the true pelvis remained unchanged.

External boost vs. brachytherapy

43 patients with stage IIIB and IVA disease received external radiotherapy boosts of 20Gy/5fractions. A portion of the rectum would therefore have received an ID2

dose of 93Gy (a/b=3). Nineteen patients with stage IIB cervical cancer received 18Gy in 6fractions as an external boost dose, with a total ID2 dose of 80Gy. This unconventional and highly controversial method was done due to the fact that the hospital had no brachytherapy machine in working order, and was unable to purchase new equipment due to lack of funds. Brachytherapy was started late in 2000 after the hospital negotiated the services of a brachytherapy machine from a private institution. Most patients are now subsequently treated at this particular private institution regarding HDR boost.

Follow-up and Endpoints

The median time of follow-up was 15.3 months. Patients who did not visit regularly were contacted via telephone and/or letter. The onset, cessation, duration, and severity of rectal complications were recorded. We unfortunately did not have data on the exact grading of proctitis.

The diagnosis of late radiation proctitis was made clinically in patients who received radiotherapy in the previous 24 months and presented with fresh or altered blood in the stools, which increased in frequency. Recurrence of cervical carcinoma was excluded by pelvic examination, with all suspicious lesions being biopsied.

Statistics

Comparisons of patients and treatment characteristics between the two groups were calculated by x^2/Fisher's exact test for categorical variables.

Table 1: Patient characteristics

	Proctitis [29]	non -proctitis [33]	
Stage:			
IIb	7	12	
IIIB	20	19	p=0.018
IVA	2	2	
Age:			
<40 years	6	5	
>40 years	23	28	p=0.118
HIV-status:			
+	2	9	
-	17	22	
unknown	10	2	p=0.211
Blood transfusion:			
Yes	14	12	p=0.374
No	15	21	

Table 2:

Radiotherapy dose (total + boost):

	Proctitis [29]	non-proctitis [33]	
Whole pelvis irradiation			
42[40] Gy/14[16] fractions			
+			
True pelvis irradiation			
12Gy/4fx			
+			
Boost dosage			
20Gy/5fx	24	24	p=0.0512
or			
18Gy/6fx	5	9	

Results

The median age was 53.8 [range 32-83 years].

Nineteen patients had Stage IIB cervical cancer, 39 patients had Stage IIIB, and 4 patients had Stage IVA disease.
The HIV-status in 12 patients was unknown. Eleven patients were HIV positive and 39 patients HIV-negative.

Patient characteristics and radiation dosage and type are listed in tables 1 and 2.

62 patients received radiotherapy for stage IIb – stage IVa cervical carcinoma for a period of time not exceeding 7.5 weeks from January 1999 to December 2000. The mean follow up time was 15.3 months.

Fourteen patients were lost to follow up [no contact with patient for longer than 1 year] and 4 patients died. They were included in the study as they were seen at least once in 6 months.

Of the 62 patients treated, 29 [46.77%] developed late radiation proctitis. In the proctitis group, 9 patients [12.5%] needed surgical intervention.
Seven patients required colostomies for severe rectal bleeding. Two patients had recto-vaginal fistulae with severe late radiation proctitis and required laparotomies.

We found a significantly greater incidence of radiation proctitis in stage IIIB cervical carcinoma [p=0.018]. The higher dose per fraction, especially of the original boost [5Gy per fraction], must have significantly contributed to this finding. It should also be noted that stage III disease is an independent risk factor for rectal complications, but this is unlikely in our study based on radiobiological effects of hypofractionation.

No significant difference was found in the <40 year age group compared to the >40 year age group.

Whether the patients received a blood transfusion or not also made no statistical difference [p=0.374].

We had information on the HIV-status in less than 65% of our population in the proctitis group and less than 90% in our non-proctitis group. Therefor our data is invalidated in this respect.

A definite trend towards an increase in late radiation proctitis was found in the patients receiving irradiation to the true pelvis of 20Gy/5fractions [p=0.0512], although it was not statistically significant. 75% of these patients also received the highest whole-pelvis irradiation dose, being treated before May 2000. These patients therefore comprised the group with the highest dose of EBRT.

Discussion

Radiation therapy is a very effective treatment for patients with locally advanced carcinoma of the uterine cervix. It is also an alternative to surgery in Stages I-IIA, with comparable survival and tumour control being reported with either modality.[15]

There are many reports about the complications of radical radiotherapy for cervical cancer[9, 16, 17]. The majority is gastrointestinal and urinary complications. Small and large bowels were usually included in the analysis of gastrointestinal sequelae in early reports.

Due to the improvement of therapeutic technique and a decrease in the dose per fraction, incidence of small intestinal complications had decreased in patients with radiation alone.

Because the rectum is near the uterine cervix and its tolerance [$TD_{50/50}$] is about 60 Gy, [18] complete avoidance of rectal complication is impossible using radiation alone.

In radiotherapy of cervical cancer, both external beam radiotherapy and intracavitary brachytherapy can result in late radiation proctitis. There are various investigators that have noted a correlation between external pelvic dose and rectal complications.

Montana and Fowler[10] reported a 3% incidence of late radiation proctitis with external beam radiotherapy [EBRT] <20 Gy, 12% with 20-40 Gy and 14% with > 40Gy [p=0.02]. Roeske ET al.[19] found that EBRT dose was a significant factor associated with the risk of late rectal sequelae. Stryker ET al[11] also reported that EBRT total dose was a significant prognostic factor of Grade 2-3 rectal complication on multivariate analysis.

Using the ID2 tables for late effects, we found that the patients that developed radiation proctitis had received EBRT doses of between 80 Gy (in stage IIB after March 2000), and 93 Gy (in stage IIIB prior to March 2000). Our results would support the influence of EBRT total dose on rectal complication.

Significant more patients with stage IIIB cervical cancer developed late radiation proctitis [p=0.018].
Choi et al. demonstrated that stage III disease was an independent risk factor for developing rectal complications.[20] Roeske et al. found that locally advanced stage [IIB-III] was a risk factor in univariate analysis but not multivariate

analysis.[19] Perez et al[21] reported 3.4% grade 2-3 proctitis among Stage IB-IIB patients receiving radiotherapy alone. It is more likely in our study that the increase in late radiation proctitis is due to the higher EBRT dose and the higher dose per fraction, especially that of the boost, given to patients with stage IIIB.

Dose fractionation is also an important factor that correlates with incidence and severity of sequelae. Several authors, including Fowler[22] and Withers ET al.[23] have shown in experimental data the substantial impact of higher dose per fraction on late effects of irradiation on healthy tissues.

Sherra-Davies[24] reported greater morbidity when patients were treated with higher daily fractions of external-beam irradiation [40 Gy/16 fractions over 3 weeks].

At Pretoria Academic Hospital 3Gy fractions were used to due to the number of patients being referred for treatment. This was prescribed for patients requiring both radical and palliative treatment, provided performance status was acceptable. The waiting time before treatment is between 3-4 weeks per machine. It was felt that hypofractionation may well offer a reasonable solution to this problem. Planning and machine staff shortages also contributed to the problem.

An incidence of radiation proctitis of 46.77% is cause for concern, especially as 12.5% required surgical intervention.

The results of this study support subsequent changes in departmental policy as regards the radiation of patients with locally advanced cervical cancer. It was suspected that the EBRT total dose and high dose per fraction contributed to the frequent occurrence of radiation proctitis observed in our patients. This led to a change in departmental protocol from March 2000: 40Gy in16fractions whole-pelvis irradiation in stage II and III cervical carcinoma with additional true pelvis

irradiation of 12,5Gy in 5 fractions, followed by HDR boost. This was subsequently changed in June 2001 to 45Gy in 18 fractions to the whole pelvis and 7,5Gy to the true pelvis followed by HDR boost.

Huang ET al.[25] suggested that diminishing the percentage of EBRT doses on the central and parametrial pelvis may be considered for reducing rectal complications in future. This is usually achieved with a midline blocking during the course of EBRT, prior to intracavity brachytherapy. This method could not be employed at our institution during the period of study since brachytherapy was not available. It is accepted that there is a definite reduction in survival (up to 50%) in cases where brachytherapy is omitted from the treatment regime, for whatever reason, and substituted with external boosts. In treatment regimes that employ this method, many patients may in fact be receiving palliation rather than curative radiotherapy. Our study was not designed to determine survival and thus this cannot be substantiated in our department.

According to our results, decreasing EBRT total dose and dose-per fraction was helpful in decreasing the incidence of radiation proctitis. Of considerable importance is that the crude incidence rates, as reported in this study, probably underestimates the true incidence. Actuarial methods are known to give a more accurate reflection of incidence.

The majority of our patients are from rural areas where access to medical assistance is severely lacking. The identification of contributing factors to late radiation proctitis is therefore essential. Preventing these severe symptoms, especially in patients where the disease is not curable, can be regarded as an important palliative manoeuvre in our patients with locally advanced cervical cancer.

Further studies are needed to investigate the role of HIV-status and AIDS (and probably CD4 count) on the incidence of radiation proctitis.

More evidence is needed on the cost-effectiveness of using hypofractionated radiotherapy in resource-constrained departments where large numbers of patients with locally advanced cervical cancer present for treatment, both radical and palliative.

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