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RESEARCH ARTICLE

Role of Colonoscopy in Management of Symptomatic Chronic Radiation Proctopathy (CRP) after Pelvic Radiotherapy (PRT): A Clinico-endoscopic Study

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Abstract

CRP is an unfortunate dreadful complication of PRT. This work represents an experience in management of CRP presented with haematochezia. A total of eligible 27 patients with a histopathologically confirmed CRP referred for management of haematochezia Patients were subjected to thorough history taking, clinical examination, traditional laboratory investigations and colonoscopic evaluation. Enrolled patients were interviewed and their symptoms were recorded prior to and after therapy and graded based on RTOG/EORTC for rectal toxicity scales. Patients were treated with ERBE Argon Plasma Coagulator ICC 200 (Tubingen, Germany) in the emergency setting and further weekly basis. Resolution of the haemorrhagic lesions and haematologic improvement occurred after performing a total of 54 sessions. Minor adverse effects [(8/27(29.62%)] were observed in the first week and no serious complications including symptom relapse within one year follow-up.

INTRODUCTION

It has been estimated that approximately 50% of cancer patients will, at some time, undergo curative or palliative radiotherapy (RT) with subsequent increased population risk of radiation injury.[1] PRT is a common therapeutic modality for carcinoma of the female genital tract, prostate and bladder. Collateral damage to organs in and/ or surrounding field of radiation resulting from high doses of radiation, would probably have detrimental effects on the therapeutic outcome of RT.[2,3]

Therapeutically, radiation energy kills cancer cells by introducing various degrees of deoxyribonucleic acid fragmentation and plasma membrane disruption; leading to either immediate or delayed cell death. However, the incidence of radiation-related deleterious complications on the host tissue nearby the tumor is difficult to determine.[4] Direct radiation injury and / or indirect through increased generation of free radicals would account for the radiation-related damage of the rapidly dividing host cells. Defective gap junctions in irradiated cells may result in abnormal cell-cell signaling, which promote multistep carcinogenesis. Cytokine release and concomitant surgery are also associated with tissue injury and ultimately fibrosis in previously irradiated tissues.[5]

Radiation anorectal injury after PRT for non-intestinal cancer is a significant cause of morbidity that may limit the required treatment dose.[6] The rectum is the most common site affected after PRT due its anatomic close proximity to pelvic organs and its relatively fixed position within the field of irradiation.[7] Acute radiation proctopathy occurs in 30% of patients up to 6 wks after completion of the radiation dosage. While, CRP is characterized by persistent or newly apparent local symptoms and endoscopic features 6-12 month after conclusion of RT.[8-10] Acute rectal radiation injury results from the death of mitotically active intestinal crypt cells, whereas CRP is a result of end arteritis obliterans, leading to hypovascular, hypocellular, hypoxic tissue formation.[11] Thus, subtle changes on the

mucosal surface often represent involvement of deeper structures; in particular, the microcirculation and consequently, radiation damage tends to be underestimated.[4]

Haemaochezia is the most common presentation; however, the true incidence of CRP is unknown as many local symptoms may be masked by patients' fears and physicians' concerns about the immediate life-threatening complications or the metastatic disease.[4]

For management of CRP, a wide range of available therapeutic options are directed primarily to control haematochezia and the other associated symptoms.[12] However, medical therapy for late cases is unsuccessful and surgery is not the first choice because of its post-operative hazards and uncertainty of the outcome.[9]

There are limited local data about CRP and its management. Therefore, we aimed to evaluate the role of colonoscopy in management of patients with CRP presented with haematochezia.

Patients and methods

A total of eligible 27 patients with a histopathologically confirmed CRP referred for management of haematochezia at the Mansoura University Outpatients' Medical and Surgical Clinics during the period between January 2010 - December 2012, were enrolled after ethical approval and giving a well-informed consent

We excluded those with inflammatory bowel disease, peripheral vascular disease, internal haemorrhoids grades (3 &4), and those without history of PRT.

Enrolled patients were subjected to thorough history taking, clinical examination, and traditional laboratory investigations. Patients were further interviewed and their symptoms were recorded prior to and after therapy and graded based on RTOG/EORTC for rectal toxicity scales. Medical records were used to collect demographic data, previous remedies, co-morbidities, previous abdomino-pelvic surgery, previous PRT dosage, and CRP latency period that was defined as the time elapsed between the diagnosis of CRP and completion of PRT dosage. Colonoscopy has been performed in all cases, with a standard colonoscope (CF130L or CFV70L; Olympus Optical Co., Ltd., Tokyo, Japan), under conscious sedation, with a 100% caecal intubation rate, to map the proximal extent of the radiation-related lesion and to visualize any other possible associated proximal pathological findings.

Patients were prepared by parenteral fluid therapy, and phosphate enema. The diagnosis of CRP was based on the colonoscopic features, histopathological diagnosis, and prior history of PRT, with a latency period more than 10 months to avoid remote risk of acute injury and nullify the possibility of fistulization.[13,14]

CRP is defined as damage to the rectum / or sigmoid colon resulting from RT to the adjacent pelvic organs for pelvic malignancies.[12] Endoscopic examination reveals mucosal pallor, friability and telangiectasia, erosions, as well as two pathognomonic histopathological criteria; ecstatic blood vessels and hyalinated lamina propria, according to Tsang and Rotterdam modification.[15]

Patients were further weekly treated with ERBE Argon Plasma Coagulator ICC 200 (Tubingen, Germany). A 1-2 L/min argon flow rate, with frequent air aspiration, a 40-60 W electrical power setting, and 2-3 mm diameter probes were used during the APC procedure. Bleeding telangiectatic lesions were coagulated first, in a dotted manner, in a forward viewing, then, we proceed with the colonoscope in the retroflexed position to complete the session. Patients are instructed to come back if bleeding persists, then, discharged with a follow-up card and a prescription of laxatives, haemostatics, and haematinics, according to circumstances.

APC-related adverse effects were defined as the occurrence of nausea, vomiting, ano-rectal pain, fever, flushing, and bladder symptoms within one week after an APC session. Patients were considered as responders if the hemoglobin (Hb) level increased 10% from baseline or complete normalization of the Hb level (in men; >130 g/L, and in women; > 115 g/L) without the need for blood transfusion.[16]

Statistical analyses were conducted by using statistical software (Statistical Package for Social Sciences (SPSS), version 15.0; SPSS Inc., Chicago, IL, USA). The Student's t-test and x^2 tests were used to compare data as appropriate. A p-value of ≤ 0.05 was considered to indicate statistical significance.

Results

A total of eligible 27 histopathologically proven CRP patients (15M, 12F), and presented all with haematochezia were enrolled. Their primary irradiated cancer sites are prostate (9), cervix (7), and bladder (8), vagina (1), and endometrium (1). Of them (9) patients (33.33%) received previous medical therapies and none of them was endoscopically manipulated. Failed medications used included; steroid enemas, mesalazine/ 5-ASA suppositories, lopearmide. Smoking habit appears significantly common in males. Otherwise, there is no significant difference between male and female participants' groups regarding age, BMI, onset of symptoms, radiation dosage, previous medications and associated co-morbidities. Detailed patients' characteristics are displayed in Table 1.

Our patients presented with haematochezia [(n.=27 (100%)], faecal incontinence [(n.=11 (40.74%)], abdominal pain, anorectal pain, constipation, and diarrhea [n.= 3(11.11%), n.=1(3.7%), n.= 3(11.11%),1 (3.7%); respectively]. Haematochezia was the only presenting symptom in 16 patients (59.25%) while 5 patients (18.51%) had 2 symptoms, 4 patients (14.81%) had 3 symptoms and the last 2 patients (7.4%) presented with 4 symptoms. After APC, 8 patients (29.62%) experienced the following symptoms; rectal bleeds, rectal pain, transient urine retention in [n.= 1(3.7%), n.= 6 (21.8%), n.=1(3.7%); respectively] as shown in Table 2.

Colonoscopy has been performed in all cases with a standard colonoscope. CRP was the sole diagnosis in 16 patients (59.25%). The remaining 11 (40.74%) cases have multiple diagnoses ranging from [2 in (n. = 5 cases), 3 in (n. =2 cases), and 4 in (n. = 4 cases)]

Endoscopic findings include; 11 patients (40.74%) with internal haemorrhoids, 4 patients (14.81%) had colonic cancer (one at recto-sigmoid junction and 3 at the sigmoid colon), 3 patients (11.11%) had colonic polyps, 2 patients (7.4%) had non bleeding colonic diverticulosis in the descending colon, and 2 patients (7.4%) had angiodysplasia at the ascending colon (Table 3).

Resolution of the haemorrhagic lesions and haematologic improvement occurred after performing a total of 54 sessions (an average 2 sessions per patient) as follows; one session in 6 (21.8%) patients, 2 sessions in 17 patients (62.96%) and 3 sessions or more in the last 4 patients(14.81%). Single-session response rate 6/27(22.22%) and an overall success rate of 26/27(96.29%) Minor adverse effects [(8/27(29.62%)] were observed in the first week after APC as follows; rectal bleeds in 1 patient1 (3.7%), anorectal pain in 6 patients (22.22%) and transient urine retention in 1 patient (3.7%). Perforation, fistula, stricture formation and symptom relapse were not reported within one year follow up. Rectal bleeding persists in only 1 patient (3.7%) with compensated chronic liver disease and controlled after hospitalization, and received an extra APC session. Parenteral fluids, tranexamic acid, vitamin K, and fresh blood transfusion (2 units) were also given. Endoscopic polypectomy was done for 3 cases (11.11%) successfully. Suspected cancer patients [4 (14.81%)] were biopsied , and 2 patients (7.4%) with angiodysplasia were ablated by APC, while 2 cases (7.4%) with colonic diverticulae were not bleeding and left untouched.

Regarding the haematological parameters, mean pre-treatment Hb level 81g/L and post-treatment Hb level 107 g/L where 3 males had Hb level) 130, 2 females had a level 115g/L and 21 patients(77.77%) had 10% Hb increase without the need for blood transfusion.

Table 1: Patients' Characteristics and Demographics

Parameters	Males (n.=15)	Females (n.=12)
Age (Ys)	67±1.3	69±2.1
Gender(M/F)	15	12
BMI(Kg/m^2)	23.±0.9	24±0.3
Urban/ Rural	11/4	9/3
Smoking (+/-)	13/2*	2/10
Primary tumor sites		
Prostate/Testicle	9/1	0/0
Cervix/ Vagina/Endometrium	0/0/0	7/1/1
Bladder	5	3
Onset of symptoms after RT (Ys)	1.9(1.3-11)	1.8(1.5-12)
Radiation dose given	5100±200 cGy	5200±300 cGy
Previous therapy	6	3
Co-morbidities		
Chronic liver disease	2	7
Hypertension (HTN)	7	6
Diabetes mellitus (DM)	6	5
Renal impairment	4	5

*p-value < 0.01

Table 2: Patients' Initial Presentation

Parameter	N. (%)
Haemotochezia	27 (100%)
Abdominal Pain	3 (11.11%)

Anorectal pain	1 (3.7%)
Faecal incontinence	11 (40.74%)
Diarrhoea	3 (11.11%)
Constipation	1 (3.7%)
RTOG/EORTC Toxicity Grade: 1/2	19 (70.4%/ 8 (29.6%)
Secondary Symptoms	
Rectal bleeds	1 (3.7%)
Rectal pain	6 (21.8%)
Bladder symptoms	1 (3.7%)

Table 3: Endoscopic Findings

Endoscopic Diagnosis	N. (%)
Chronic radiation proctopathy	27 (100%)
Alone	16 (59.25%)
Associated	
Diverticular disease	2 (7.4%)
Internal haemorrhoids (Grades : I,II)	11 (40.7&)
Colonic polyps	3 (11.11%)
Colonic cancer	4 (14.8%)
Angiodysplasia	2 (7.4%)

Table 4: APC and its Outcome

A P C- related parameter	N. (%)
Number of sessions	54
Mean number of sessions	2
Single session responders %	6(18.51%)
Increased Hb% > 10% without transfusion	26(96.3%)
Minor adverse effects	8(29.63%)
Success rate %	26(96.3%)

Discussion

CRP is an unfortunate complication with a considerable mortality rate that has received more attention with the increasing utilization of PRT for pelvic malignancies.[17,18]

The gastrointestinal tract is variably affected by radiation and the rectum is the most commonly affected site.[19] Few months after RT, manifestations related to rectal ischemia and fibrosis due to progressive obliterative endarteritis that pathologically appears as subintimal thickening, subendothelial accumulation of foam cells, and hyalinization of the rectal arterial wall with subsequent vascular narrowing.[20]

CRP can develop either as a consequence of non-healed acute rectal injury or after a latent period of at least 90 days.[11] Denham et al. reported that patients who experienced acute proctitis were at least twice to develop more severe late RTOG/ EORTC grades than patients who did not.[21]

Coia et al found a latency period of about 3-12 months prior to symptom development depending on the site of radiation injury.[19] The peak incidence is 6-24 months after radiation exposure.[22] But symptoms may be delayed as 20-30 years. [13,23]

About 85% of cases present within the first 2 years after RT. Estimates from retrospective data suggest that 2-20% of patients who receive PRT may be at risk of developing CRP.[24,25]

In CRP, a wide range of patient symptoms usually begin 1-2 years after RT, ranging from mild to severe and disabling.[4,25] Haematochezia is the most common symptom occurring, in up to 72%-80% of cases[26,27] due to rupture of radiation- induced telangiectasia as well as oozing from the friable, ischaemic mucosa.[12] Rectal bleeding impairs patients' daily activity and quality of life[28] especially in those with significant anaemia and transfusion dependency.

Faecal incontinence is a frequent cause for gastroenterologic consultation after PRT.[29] Sphincter dysfunction may occur in the setting of CRP due to reduced rectal compliance, sensory and motor dysfunction.[30] Manometry may reveal decreased resting pressure, reduced maximum squeeze pressure and abnormal rectoanal reflex. [31]
Prostate cancer is the most common malignancy in men where about one third of cases are treated with RT when lymph nodes or the seminal vesicles are involved. RT is given as a primary therapy as well as an adjuvant or postoperatively.[8]In females, cervico-uterine carcinoma is frequently treated with radiation. The combination of external beam and intra-cavitary sources are used in advanced carcinoma of the cervix.[8] Estimates of CRP is variable in different studies; as Wang et al found an estimate of 47% of patients treated with RT for cervical cancer developed diarrhea as a late complication of PRT.[32] Other studies found a lesser prevalence (5%-20%) of symptomatic CRP.[24] Lack of uniform scoring system is an obstacle to compare results and assess the effects of different studied variables.[33]

The likelihood of developing radiation enterocolitis after RT is dose-dependent. A radiation dose of 400-4500 cGy is thought to be a triggering factor.[34] Tissue damage correlates with the total dose delivered, however, equal doses of radiation may have variable biological effects.[35] Sensitivity to radiation is different for each cell type, tumor, or tissue.[4] However, the severity of radiation disease and radiation dosage do not always correlate.[7,8,9] Higher radiation dosages may not predispose patients to severe radiation enterocolitis even after surgery.[36] Complications may be due to old age, DM, HTN, hyperlipidemia with atherosclerosis, previous history of abdomino-pelvic surgery or ongoing pelvic inflammatory disease or some chemotherapeutic agents.[37] Thus, clinicians should not spare any effort to identify patients at risk of development of CRP.
Smith et al reported that the incidence of CRP is 20% and 60% when the radiation dose is up to 7500 and >7500cGy; respectively.[38]
Chen et al found smoking as independent risk factor for development of complicated CRP.[39] Iraha et al. declared that DM, smoking, and previous pelvi-abdominal surgery are identified as risk factors for CRP requiring surgery.[40] Smoking increase patients' vulnerability to radiation injury through the enhanced release of the pro-inflammatory cytokines.[39] Concomitant radiation uropathy may indicate the existence of extensive disease and further liability to radiation injury.[39]

Radiation promotes carcinogenesis as seen in atomic bomb survivors, irradiated patients with testicular tumors and Hodgkin's disease.[41-43] Also William's et al found a high frequency of advanced gut neoplasia in their irradiated case series.[44]
Castro et al proposed 4 criteria to characterize radiation-induced cancer; 1) Tumor localization at the RT site, 2) frequent symptomatic and clinically documented chronic proctocolitis, 3) post-RT >10 years, 4) histopathological proof of radiothrapy-related alterations in the involved bowel segment.[45] Four patients in our study satisfied most of Castro's criteria. Regarding the incidence of second cancers after PRT, several studies gave contradictory reports.[46-48] However, Levitt and Caporale et al agreed to perform endoscopic surveillance for irradiated gynecologic cancer survivors.[49-50]

Diverse therapeutic options for rectal bleeding in CRP patients have been proposed and method selection is based on RTOG/EORTC; rectal toxicity scales where grades 2, 3 and grade 1 refractory to medical treatment could benefit from the endoscopic therapy. Among them, APC method appears to have promising results.[51]
APC is an innovative non contact electro-coagulation technique used to treat hemorrhagic gastrointestinal malformations by delivering high frequency, mono-polar electrically conductive argon gas.[12,16,52.] APC has an advantage of low cost, its mobility, minimal complications and limited tissue penetration (2-3mm).[53]
Our data revealed resolution of rectal haemorrhagic lesions, haematologic improvement with no serious complications. Thus, our results are in line with those previously published reports that have declared the efficacy and safety of APC in treatment of haematochezia in CRP. [54-56]
Considering the significance of CRP, improving radiation delivery, proper use of radioprotection, optimizing the radiation dosage to cancer patients, would probably decrease the incidence and severity of CRP. A high index of suspicion regarding gut symptoms after exposure to PRT is required for early diagnosis. Proper management of associated risk factors, use of antioxidants, nutrients could be of paramount importance to ameliorate acute cases and probably halt disease progression.
In conclusion; our data highlighted the diagnostic and the therapeutic value of colonoscopy in CRP patients with haematochezia. Moreover, complete colonoscopic evaluation would be strongly advised to detect any associated probable proximal pathological lesions

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