RADIATION INDUCED PROCTOCOLITIS - RISK FACTORS & CORRELATION OF SYMPTOMS WITH COLONOSCOPY

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CERTIFICATE

Certified that the dissertation titled **"RADIATION INDUCED PROCTOCOLITIS - RISK FACTORS AND CORRELATION OF SYMPTOMS WITH COLONOSCOPY"** is a bonafide work done by **Dr.A.ARAVIND,** Post graduate in Medical Gastroenterology under my supervision between June 2003 to February 2006 and is being submitted for the partial fulfillment of the requirement for the awarding of D.M. (Medical Gastroenterology) by T.N. Dr. MGR Medical University, Chennai.

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CONTENTS

1. INTRODUCTION

Although over a century has elapsed since the first description of deleterious effects of radiation on normal tissues , such effects remain the principle limitation of radiotherapy. Although current powerful radiation sources could be effective in destroying most, if not all, tumors, no ideal method exists to deliver radiation to cancer exclusively and spare normal tissues. Radiation is used as part of treatment in more than half of all cancer patients . Incidence of severe radiation-related complications is difficult to determine, long periods of follow up are required. Local symptoms may be underestimated, because physicians and patients may be more concerned with metastatic disease or immediately life-threatening conditions. Compared to studies that address the efficacy of radiotherapy, few studies exist in which complications are approached methodically and as the primary focus. Nevertheless, radiation damage to normal tissues can be costly and have not only a major impact on quality of life but also on overall survival.

Rather than discussing benefits of radiotherapy, this thesis article reviews radiation damage to normal tissues, including basic science aspects, and focuses on the most severe anorectal complications of radiotherapy. Recognition and treatment of associated lesions, including cancer recurrence, are crucial for obtaining satisfactory results.

Types and sources of radiation

Forms of radiation used clinically include X-rays, gamma (c)-rays, beta (b)-rays, and electrons . X-rays and c-rays are examples of electromagnetic radiation; b-rays and electrons are particulate radiation. As these forms of radiation interact with tissues, ionic radicals are released; Thus the term, `ionizing radiation.' Radiation is measured in Grays

(Gy). One Gy is defined as the absorbed dose of energy per kilogram of soft tissue, and is equal to one Joule per kilogram. The rad was used previously, and corresponds to one centigray (100 rad. 1 Gy). External beam radiotherapy uses megavoltage photon irradiation delivered by Cobalt-60 (c-rays) sources or high-energy linear accelerators (X-rays). The latter have been preferred for abdomino-pelvic malignancies because of a potent effect on deep tissues with minimal skin toxicity. Brachytherapy uses sources adjacent (cavitary) or within (interstitial) tumors, which permits delivery of high doses of radiation to the area surrounding the source; e.g. up to 200 Gy can be delivered in endocavitary uterine brachytherapy (with a high risk of severe damage to surrounding tissues). Cesium-137, Iridium-192, Iodine-125, and Gold-198 are isotopes used commonly in brachytherapy. [1]

Radiotherapy courses are combinations of dosage, length of time, and physics used. For most protocols in clinical use, these variables have been established empirically.

Dose fractionation and limited-field irradiation are techniques intended to minimize the risk of injury to normal tissues while maintaining a high likelihood of tumor control. Conformal techniques, which include cast-immobilization, tri-dimensional tumor definition, and individually defined radiation fields, also aim at reducing injury to normal tissues.

PATHOPHYSIOLOGY OF RADIATION DAMAGE

Radiation damage begins with disruptions in deoxyribonucleic acid (DNA) and intracellular membranes. Subsequent changes in cells, tissues, and organs depend on the extent of those initial molecular breaks and efficiency of cellular mechanisms of repair. Small DNA disruptions may be repaired readily, allowing the cell to maintain its function

and ability to divide. Some of these breaks, however, may be sufficient to induce mutant genes. If such mutants are among cell cycle regulatory genes, for example, their expression may lead to long-term malignant transformation. Severe damage to the DNA molecule results in immediate arrest of cell division, with cell death. In normal tissues, such extensive damage is manifested as depletion of an entire population of cells and long-term fibrotic changes[2] . Cells that sustain intermediate degrees of DNA disruptions may continue to divide temporarily, but mutations transmitted to their progeny eventually cause cell death.

Cells with short mitotic cycles, or undergoing active mitosis, are more likely to be damaged. `Acute reactants', such as intestinal mucosal cells are involved in acute, transient, radiation toxicity are characterized by high proliferation rates. `Late reactants', such as endothelial and smooth-muscle cells involved in chronic radiation injury divide slowly. Although the phase of the cell cycle can influence the response to irradiation, any cell, at any point in the cycle, can be damaged by high doses of radiation. Tissue damage correlates linearly with the total dose delivered; however, equal doses of radiation may have variable biological effects . Sensitivity to radiation is different for each cell type, tumor, or tissue.

Conventionally, toxicity for each tissue is defined as minimal and maximal tolerance doses TD 5/5 and TD 50/5, which represent the dose that leads to complications in 5% and 50% of patients within five years, respectively. The rectum, with TD 5/5 of 55 Gy and TD 50/5 of 80 Gy, is more resistant to radiation than the colon and small bowel, both of which have TD 5/5 of 45 Gy and TD 50/5 of 65 Gy.[2]

HISTOPATHOLOGY

Acute toxicity is associated with a variety of pathological changes, detectable predominantly in the mucosa of irradiated bowel. The epithelium cannot be replaced adequately because of damage to progenitor cells; therefore, the mucosa becomes denuded within a few days after irradiation. Nuclear atypia, depletion of epithelial cells, bacterial invasion, vascular congestion, edema, and hemorrhage can be noted. Cellular changes may be noted in crypts of the colon and rectum, and include abnormal mitotic figures and nuclear fragmentation of epithelial cells. Inflammation and crypt abscesses also occur, associated with neutrophilic infiltrates, mucosal congestion, and atrophy of villi[3]. Electron 2s[4].

Ulcerations and shallow erosions are common results of chronic ischemia. The columnar epithelium surrounding ulcerations is attenuated, and the crater characteristically contains neutrophils, lymphocytes, plasma cells, histiocytes, and eosinophils within granulation tissue. Erosion into vessels may result in gastrointestinal bleeding and anemia. Deep fissures and ulcers may lead to perforation, fistulization, abscess, or peritonitis. Nonhealing rectal ulcers are usually associated with extensive areas of fibrosis. Anal sphincter biopsies of patients with anorectal dysfunction after radiotherapy demonstrate damage to the myoenteric plexus and smooth-muscle hypertrophy [5.]

The fibrosis after bowel irradiation also may involve the submucosa, muscular layers, and serosa. Of note, fibrotic reaction of tissues that surround the bowel may lead to formation of adhesions and intestinal obstruction.

As in other irradiated tissues, `radiation fibroblasts' may be present in irradiated bowel. These cells are enlarged, pleomorphic, basophilic, spindle-shaped, and may be confused with malignant cells[6]. Adipose cells also may be seen within fibrous tissues. `Colitis cystica profunda' is presence of cysts lined by colonic epithelium in the submucosa or muscularis propria. Such glandular structures within the bowel wall also may be confused with cancer.

Predisposing factors

Damage to normal tissues depends upon the radiation technique, dose, volume of irradiated tissues, and patient factors. The combination of external irradiation with an intracavitary source usually carries a higher risk compared with either technique alone because of the additive effects[7]. Proximity of structures in the field, mucosal coverage, and anatomic fixation also are associated with increased susceptibility to injury.

The likelihood of radiation damage may be increased by radiosensitiers, such as Doxorubicin, 5-flurouracil, and oxygenation . Conversely, agents such as 2-mercaptopropionyl, vitamin E, and glutamine, appear to have radioprotectant properties. Adhesions from surgery or inflammatory disease predispose to damage the small bowel because of fixation .

However, inflammatory bowel disease itself does not appear to predispose the bowel wall to radiation injury. Chronic injury appears to develop more rapidly and be more severe in patients with diabetes and arteriosclerotic disease [8]. The combination of pre-operative radiation with total mesorectal excision for treatment of rectal cancer has been reported to

result in high anastomotic leak and perineal wound infection rates.

CLINICAL CLASSIFICATION

Acute, subacute, and chronic radiation injury have been defined arbitrarily as occurring within one month, between one and three months, and more than three months after radiotherapy, respectively [9]. The severity of damage has been further classified into grades of toxicity and scoring systems. These classifications aim at facilitating comparison of results from different studies. Toxicity criteria for combined-modality treatments have not yet been devised fully.

Radiation protocols causing anorectal damage

Cervico-uterine carcinoma is treated frequently with radiation. The combination of external beam and intracavitary sources is customary in advanced carcinoma of the cervix. Enteritis and recto-vaginal fistula are common complications . An analysis of 1801 patients treated between 1962 and 1982 showed a progressive rise in radiation-induced bowel disorders, including rectovaginal fistula; late complications that required surgical consultation occurred in 4% of patients[10]. Another study reported a 17% incidence of moderate or severe complications in patients who underwent pre-operative brachytherapy in combination with external beam for carcinoma cervix [11]. The sigmoid colon was involved most frequently, followed by the rectum and genitourinary organs. Analysis of a series of 831 patients with cancer of the cervix showed a linear correlation between the incidence of small-bowel complications and doses of radiation delivered[12] . Similar observations have

been made in relation to colonic injury.

Radiation is a major treatment modality in patients with carcinoma of the vagina . In a report of 165 patients who received total doses of 80±120 Gy, rectovaginal or rectovesical fistulas developed in 4% of patients . The accepted TD 5/5 for ulceration of the vagina is approximately 90 Gy and for fistula formation, greater than 100 Gy ; however, a threshold dose of only 80 Gy has been reported for development of a rectovaginal fstula [13.] Tumour stage and location in the vagina influence these variations.

Approximately 30% of prostate cancers are treated with radiotherapy. With external beam alone, acute gastrointestinal effects occur in 30% to 40% of patients and usually develop within four weeks of therapy. Diarrhea, rectal discomfort, and tenesmus lead to interruption of therapy in approximately 5% of patients. [14.] Chronic complications diarrhoea, rectal ulcers, strictures, and fistula affect approximately 12% of patients and may lead to surgical intervention in 1% of patients . Severe late complications were noted in 3% of patients in one study.

DIAGNOSIS OF RADIATION DAMAGE

When radiation is given in sufficient amounts to kill a tumour, one can presuppose some degree of damage to normal tissues, with variable clinical significance. The most frequent complications the colorectal surgeon encounters are skin and wound problems, radiation enteritis, proctocolitis, fistulization, and stenosis. Late manifestations do not correlate with the incidence of acute toxicity.

Acute dermatitis involving the perianal area, buttocks, vulva, and perineum may be asymptomatic or cause itching, burning, and pain. Examination discloses erythema, maculo-papular changes, vesicles, or ulcerations.

Using approximately 5 ´ 2 Gy/week fractionation, erythema usually appears between the third and fifth weeks of treatment, and becomes more accentuated and painful thereafter. Associated oedema and moist desquamation may develop. Severe reactions are rare and characterized by ulceration, haemorrhage and necrosis. After healing occurs, the new skin is usually erythematous for several weeks, followed by hyperpigmentation that resolves over several months.

Chronic radiodermatitis frequently causes sensation of dryness, but hyperesthesia and significant pain also may occur. Findings include hyperpigmentation or depigmentation, hyperkeratosis, epilation, atrophy, fibrosis, telangiectasis, oedema, ulceration, and necrosis. Squamous cell carcinoma may develop years later.[15]

Radionecrosis, involving the anodermis or entire anal canal, may develop within the first two weeks following irradiation for anorectal or, rarely, gynaecological malignancy.

Patients may report pain, constipation, and rectal bleeding. Fever, and perianal and perineal necrosis and infection, may develop[16]. Examination under anaesthesia is required to determine extent of tissue damage. Oedema, sphincter spasm, and necrosis are common findings.

Acute proctitis most often causes tenesmus and bloody mucus discharge.

Proctosigmoidoscopy discloses oedema, inflammation, and friability of the mucosa.

These manifestations tend to resolve within a few weeks, as in acute colitis or enteritis. If the proctitis is extensive, one should seek other sites of injury (e.g. in the vagina, urethra, and bladder). Whether diarrhea is due to intestinal injury or impaired rectal function can be difficult to determine[17]. In radiation enteritis or colitis, contrast studies may show non-specific mucosal changes, areas of thickening and stenosis, and decreased peristalsis[18]

On endoscopy; the mucosa is pale and telangiectatic. In chronic proctitis, symptoms usually begin approximately one year after radiation, and can range from mild to disabling[19]. Hemorrhage, ulceration, perforation, fistulization, and stenosis can occur. On proctosigmoidoscopy, the mucosa is pale, telangiectatic, and friable. In cases of rectal or anastomotic strictures, the first concern is to rule out tumour recurrence. Ulceration on the anterior wall of the rectum also may be difficult to distinguish from recurrent rectal cancer after low anterior resection or prostate cancer after prostatectomy. Biopsies and imaging studies are necessary. Barium enema may help define the severity and location of a stenotic 2 sphincter defects.

In the differential diagnosis of radiation-related lesions, tumor recurrence or radiation-induced de-novo neoplasia should be ruled out. In addition, cytomegalovirus (CMV) coloproctitis, perianal herpetic eruptions, and bacterial infections that result from immunosuppression secondary to cancer or chemotherapy may occur in irradiated areas.

The role of these infections is essential to determine because they usually respond to specific therapy. Other important conditions that may be confused with radiation injury are Crohn's disease, atherosclerotic ischaemic colitis, tuberculosis, and lymphoma.

Given the disparity between acute and chronic effects, and inability to predict eventual manifestations of late injury, frequent follow-up visits are recommended. Surveillance should include at least a thorough history, routine physical examination, gynecological and rectal examinations, and proctosigmoidoscopy. Colonoscopy, imaging, biopsies, and microbiology are used selectively.

Endoscopy and barium enema should be performed with special caution because of increased risk of iatrogenic perforation of irradiated areas. Although histology is often necessary to establish the diagnosis with certainty, biopsies also must be taken with particular caution.

Newer diagnostic modalities like high-resolution MRI, Endosonography and defecography can provide important imaging data for anorectal problems.

PREVENTION

Total protection of normal ano-rectal structures during radiotherapy remains elusive. No significant data exist to support the use of prophylactic medications. Hyperbaric oxygen has been used after radiotherapy as an attempt to reduce progression of radiation-induced lesions. The use of a high proton energy source can prevent damage to the skin. Strict compliance with current radiotherapy standards, including conformal techniques,

fractionation, and control of equipment, should help in decreasing the risk of complications [24].

Prevention of damage to the small bowel and sigmoid colon is achievable because such structures normally are mobile. Several methods have been proposed, including surgical pexy and implantation of breast-type or balloontype spacers. Non-surgical approaches also have been shown to be effective: for example, the so-called `belly board', a mattress with a hole on which the patient's abdomen is placed (in the prone position), has been reported to reduce small-bowel injury[25,26] . Effective prevention of radiation enteritis has been reported with the creation of an intra-abdominal sling using absorbable mesh or peritoneum, as well as spacers.

Although such methods increase the risk of infection, internal hernias, and other complications, their use has been advocated after radiation for abdominopelvic malignancy, in particular when radiation doses greater than 45 Gy are needed. Optimal candidates would be patients with high pelvic recurrence risk, residual disease after debulking surgery, or those with unresectable tumour at the time of exploration[26].

TREATMENT

In treating radiation-induced complications, conservative measures should always be considered first. Most acute effects are reversible and require only supportive and symptomatic care, and less-severe forms of chronic injury also can be controlled effectively by medical intervention.

Dermatitis with erythema and dry desquamation is best treated by application of sulfadiazine ointments. Severe chronic dermatitis can be kept dry with eosin solution. Symptoms of acute proctitis usually respond to sitz baths, antidiarrheals, and steroid retention enemas. Mild chronic proctitis may require long-term low-residue diets, stool softeners, and 5-aminosalicylic acid or sucralfate enemas [27,28] . Even in the presence of mild rectal bleeding, most patients can be treated conservatively. For example, in a series of 109 patients who underwent I-125 brachytherapy for prostate cancer, with minimum dose at 140±160 Gy, 19% developed persistent rectal bleeding.

Resolution of bleeding occurred in all these patients with steroid enemas, laser coagulation, or reassurance alone.

Formalin therapy is a practical and effective method for treating radiation-induced cystitis and proctitis.

A prospective study showed that 80 ml of 4% formalin instilled into the rectum in 20-ml aliquots had 100% initial success in stopping rectal bleeding, with a low recurrence rate [29.]

Another approach, laser coagulation, although more invasive and expensive, also is highly effective and has the advantage of being feasible during the diagnostic endoscopy[30] . Non-operative management of chronic enteritis comprises low-residue diets, low fat or lactose-free diets, and antidiarrheal and antispasmodic drugs.

Actinic ulcerations, because of their ischaemic component, react like arterial ulcers, and similar precautions are required. Ulcerated areas should be protected from additional injury. Correction of low-flow states such as heart failure or dehydration can increase tissue oxygenation and promote healing. Skin wounds should be kept clean to avoid secondary infection, and severe mucosal ulceration and fistulas may require diversion to heal.

Many patients who receive radiotherapy are elderly, have diseases other than cancer, are malnourished, have organ dysfunction, and have had surgery or chemotherapy. Such medical conditions should be optimized. Correction of anaemia,whether by iron supplements, transfusion, or erythropoietin,improves tissue oxygen delivery and improves the likelihood of healing. Diabetes control also may be beneficial. Drugs must be used with caution. When prescribing narcotic, analgesic and antiin flammatory agents, kidney and liver functions should be monitored because cancer or side-effects of adjunctive treatment often affect these organs. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs may be exacerbated due to mucosal fragility after chemotherapy; bleeding tends to be more serious in this setting.

Dementia, depression, or high doses of narcotics may lead to poor compliance. Special care is recommended during application of enemas because radiation renders the rectum more susceptible to perforation. Overall, symptomatic control is achieved in most patients with medical treatment and reassurance.

Currently, a wide variety of pharmacological options, endoscopic cautery techniques and surgical procedures have been proposed for the treatment of chronic radiation proctopathy[31,37,38]. Although these have been proposed primarily as treatment for rectal bleeding, the control of other symptoms has been noted with some of these agents. Pharmacological options include 5-aminosalicylic acid preparations, corticosteroid enemas, sucralfate (oral, enemas), formalin, short chain fatty acid enemas, oestrogen/progesterone, hyperbaric oxygen, antioxidants, sodium pentosan polysulphate and misoprostol rectal suppositories.

Of these, sucralfate and formalin therapy appear to be effective for bleeding control. Misoprostol rectal suppositories and oral sucralfate may be useful in the prevention of acute and chronic symptoms of radiation proctopathy.

Endoscopic cautery techniques have included the use of Nd:YAG laser and argon laser for coagulation of bleeding neovascular telangiectasias. Argon plasma coagulation offers a safe non-contact method of delivering haemostasis which has proven to be particularly useful in targeting difficult to reach lesions tangentially.

Surgery is generally reserved for severe refractory cases involving ongoing haemorrhage, obstruction, stricture formation, fistulas and perforation. Given that formal randomized placebo-controlled studies are lacking for most treatments, the management of these patients is often challenging and unclear. Hence, there is a need for more research and education on radiation proctopathy.

Surgical treatment

Radionecrosis of the anal canal requires a diverting colostomy. If healing occurs, anal stricture usually ensues, which represents another challenge because most advanced techniques are not suitable for irradiated tissues. As no safe method exists to restore sphincter function after radiation damage, the best option is to leave the stoma permanently.

Most cases of proctitis respond to conservative management. A diverting stoma does not prevent progression of radiation damage in the defunctionalized segment. Proctectomy is occasionally indicated in cases of disabling tenesmus, blood loss refractory to conservative treatment, perforation, stenosis with suspected malignancy, or fistula. Younger patients with normal sphincter function may benefit from a coloanal anastomosis. In elderly patients, a Hartmann's procedure is more appropriate, and should be preferred to APR to avoid perineal wound problems.[32]

Several techniques can be used in rectal stenosis, including diverting colostomy, Hartmann's procedure, APR, low-anterior resection, coloanal anastomosis, and Bricker's repair. Dilatation can be performed manually for segmental strictures within finger reach.

For higher stenoses, a Hegar's dilator, Savary bougies, or endoscopic balloon dilatation may be adequate; however, these methods have high rates of restenosis, which requires repeated dilatations every three to four months, with an increasing risk of perforation. Other methods include transanal lysis with electrocautery, transanal proctoplasty, and endorectal use of a linear stapler for stricture of an end-to-side colo-rectal anastomosis. A diverting stoma is usually required for acute obstruction or in debilitated patients. When resection is performed, sphincter-saving procedures tend to have poor results. The distal rectal stump may be relatively ischaemic after radiotherapy, and a high risk of leakage is expected with either stapled or hand-sewn anastomoses. A coloanal sleeve anastomosis can be used in select patients, but those with anal sphincter impairmen are unlikely to benefit . This technique involves resection of the strictured segment, mucosectomy of the anal canal, and use of proximal healthy colon for anastomosis at the level or just above the dentate line. A protective temporary diverting stoma is mandatory. The rarely performed Bricker and Johnston repair involves a patch graft of proximal colon with anantimesenteric split, folded over to correct a linear stricture . Other than the authors' series of 26 patients, experience with this complicated technique,which appears to be associated with high morbidity, hasnot been well described in the literature. In the elderly or debilitated patient who needs resection, a permanent colostomy is safer than restoring bowel continuity by anyof the above methods. Radiation-induced fistulas usually require surgical intervention. Direct suture, however, is not recommended.In high, small colovaginal or rectovaginal fistulas, a pedicle graft of greater omentum can be used . The fistula is excised, edges of the bowel and vagina are trimmed, and the omentum is mobilized on a pedicle based on the right or

left gastroepiploic artery and placed between rectal wall and vagina . Another technique (Martius) uses a bulbocavernous flap or labial fat pad to cover a rectovaginal fistula . The borders of the fistula are excised and rectal and vaginal walls separated widely. The rectal defect is then closed transversely, and the fat and fibromuscular content of the labium mobilized into the fistula site through a subcutaneous tunnel. Vascular supply can be based on either the internal or external pudendal arteries. Success with this method was reported in 80% of patients . Bricker's operation could be suitable for a large fistula alone or associated with rectal stricture. However, a diverting stoma is required, and the results reported include a 50% morbidity rate and 73 satisfactory continence .The preferred option for large defects is a coloanal anastomosis. Mobilizing the splenic flexure can facilitate bringing nonirradiated left colon down to the pelvis. In low strictures, the rectum can be excised totally, or its wall left in place with no attempts to free it from the vagina. The mucosa is excised and colon threaded through the rectal muscular tubular wall and anastomosed at the dentate line. The anastomosis is protected by a diverting stoma, which may be closed approximately three months later. Full continence is recovered by 75% of the patients within one year. Although pre-operative assessment of anal sphincter function is essential when considering this type of reconstruction , much controversy exists regarding the accuracy of manometry, defaecography, and digital examination. Radiation-induced colovesical fistulas are rare, and the same procedures described above may be used in their management. Although these fistulae usually require surgical treatment, urgent surgery is not needed unless recurrent cancer is present or cannot be excluded. When a Anorectal radiation patient does well after spontaneous drainage of a paracolic abscess into the

bladder, operation can be postponed until the clinical status improves and local conditions are more favourable. Inability to rule out cancer is an indication for earlier intervention.

Small-bowel fistulas ± the ileum involved most frequently ± are often associated with radiation damage to the colon and rectum. Areas of radiation injury found in the small bowel during laparotomy for other reasons should be managed with caution. Extensive adhesiolysis is best avoided because the intestine is poorly vascularized and prone to fistulization, even when it appears thickened.

Malabsorption, secondary to extensive mucosal damage or multiple strictures, may be worsened after intestinal resection; therefore, only necessary resections should be performed, with liberal use of intestinal bypasses.

In the irradiated pelvis, anastomotic leaks with signs of sepsis or abscess formation are usually treated with drainage and proximal diversion. If the patient is eligible for future reestablishment of the continuity, a right transverse colostomy or loop ileostomy are preferable, to preserve the left colon and serve as protective stoma after reconstruction. For complete anastomotic disruption, Hartmann's procedure is the operation of choice.

When rectal cancer is treated with pre-operative irradiation, a diverting stoma is recommended for patients undergoing sphincter-saving resection after having received more than 45 Gy in less than five weeks. Similarly, after irradiation and APR within a short interval, it has been recommended that the perineum not be closed primarily.

Conclusions

Anorectum and adjacent structures are at great risk of injury secondary to radiotherapy, and no specific guidelines for treatment exist. Expertise in this complex area is difficult to achieve. Surveillance, early and precise diagnosis, and appropriate therapy are paramount in managing such complications. Moreover, the combined effects of cancer, chemotherapy, radiotherapy, and associated diseases often require multidisciplinary involvement.

Radiation damage tends to be underestimated because subtle changes on the surface often represent major involvement of deeper structures; in particular, the microcirculation. Therefore, investigation should not be limited to symptomatic or obvious lesions. Knowledge of the dose, source, and technique used for radiotherapy may help estimate the extent of damage. Healing of a radiation-induced lesion may be incomplete, and recurrent lesions from radiation endarteritis or progression of associated disorders can precipitate symptoms even in a previously stable area.

Patients with pain, or who are noncooperative with examination for any other reason, should undergo examination under anaesthesia. Despite modern imaging, differentiation between changes due to radiation, surgery, and tumor may be challenging. Invasive tests are associated with high complication rates. Pre-operative radiation for rectal cancer followed by colorectal or coloanal anastomosis is an indication for frequent follow ups, even in the presence of a protective stoma.

Medical treatment is preferred and sufficient for most radiation-induced damage to normal tissues. Surgery on irradiated areas is associated with increased risk of complications, which adds to the generally higher surgical risk of cancer patients. Quality of life can be improved significantly with less-invasive modalities; for example, laser and formalin therapy for rectal bleeding.

Cervical Carcinoma

Worldwide, invasive cervical cancer is the most common genital female malignancy and the second most common malignancy in women, after breast cancer. The estimated total number of new cases is 371,200 per year worldwide or 9.8% of all cancers in women. The disease is more common in economically disadvantaged developing countries, in which 78% of worldwide cervical cancers occur. These account for 15% of all cancers in women. The associated lifetime risk in such countries is about 3%.

Cancer of the uterine cervix is largely a preventable disease characterized by a long lead-time, with precancerous lesions gradually progressing through recognizable stages before developing into invasive disease. The disease process is almost certainly curable if it is identified prior to its progression to invasive cancer. However, invasive cervical cancer remains a disease of significant morbidity, and it is a major cause of cancer deaths in women worldwide, although its incidence and mortality rates have declined substantially (particularly in countries that have well-developed screening programs). Cancer of the

cervix in its early stages is readily managed with surgery. Radiation or chemoradiation therapies are reserved for high-risk early stages or advanced disease.

Human papilloma virus (HPV) is now recognized as the most important causative agent in cervical carcinogenesis. Cancer of the cervix typically originates from a dysplastic or premalignant lesion previously present at the active squamocolumnar junction. The transformation from mild dysplastic to invasive carcinoma generally occurs slowly within several years, although the rate of this process varies widely. The types include the following: exophytic, nodular, infiltrative, and ulcerative.

The main pathways for the spread of invasive cervical cancer consist of the following: (1) microscopic spread into vaginal mucosa beyond visible or palpable tumor; (2) extension into the endometrium or myometrium of the corpus; (3) direct extension into the parametrium and in advanced stages into adjacent structures; and (4) spread into the regional pelvic lymph nodes and potentially into the retroperitoneal, inguinal, or thoracic lymph nodes.

Squamous cell carcinoma (SCC) accounts for 80-90% of all cervical malignancies in large series[33.39]. The major histopathologic subtypes include (1) well-differentiated, keratinizing, large-cell SCC (25% of cases); (2) moderately differentiated, nonkeratinizing, large-cell SCC (70% of cases); and (3) small-cell undifferentiated carcinoma (about 5% of cases), which is associated with distinctly poor prognosis.

Pure adenocarcinomas arise from endocervical type cells and constitute 5-20% of all cervical malignancies.

Prognosis

Among the major factors that influence prognosis are stage, volume and grade of tumor, histologic type, lymphatic spread, and vascular invasion

Stages are defined by the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) or the American Joint Committee on Cancer's (AJCC) TNM classification

TNM definitions

Primary tumor (T)

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ
- **T1/I**: Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
- **T1a/IA**: Invasive carcinoma diagnosed only by microscopy.

- **T1b/IB**: All macroscopically visible lesions--even with superficial invasion.

- **T1a1/Ia1**: Measured stromal invasion 3 mm or less in depth and 7 mm or less in horizontal spread

- **T1a2/IA2**: Measured stromal invasion more than 3 mm and not more than 5 mm with a horizontal spread 7 mm or less

- **T1b/IB:** Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2

- **T1b1/IB1:** Clinically visible lesion 4 cm or less in greatest dimension

- **T1b2/IB2:** Clinically visible lesion more than 4 cm in greatest dimension

- **T2/II:** Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of the vagina

- **T2a/IIa:** Tumor without parametrial involvement

- **T2b/IIb:** Tumor with parametrial involvement

- **T3/III:** Tumor extends to the pelvic wall and/or involves the lower third of the vagina, and/or causes hydronephrosis or nonfunctioning kidney

- **T3a/IIIA:** Tumor involves lower third of the vagina, no extension to pelvic wall

- **T3b/IIIB:** Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
- **T4/IVA:** Tumor invades mucosa of the bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
- **M1/IVB:** Distant metastasis

Regional lymph nodes (N)

- **NX:** Regional lymph nodes cannot be assessed
- **N0:** No regional lymph node metastasis
- **N1:** Regional lymph node metastasis

Distant metastasis (M)

- **MX:** Distant metastasis cannot be assessed
- **M0:** No distant metastasis
- M1: Distant metastasis

TREATMENT OVERVIEW

Stage 0

Methods to treat ectocervical lesions include:

1. Loop electrosurgical excision procedure (LEEP).

2. Laser therapy.

3. Conization.

4. Cryotherapy.

Total abdominal or vaginal hysterectomy is an accepted therapy for the post reproductive age group and is particularly indicated when the neoplastic process extends to the inner cone margin

For medically inoperable patients, a single intracavitary insertion with tandem and ovoids for 5,000 milligram hours (8,000 cGy vaginal surface dose) may be used.

Stage 1

1. Radiation therapy: External-beam pelvic irradiation combined with 2 or more intracavitary applications

2. Radical hysterectomy and bilateral pelvic lymphadenectomy

Stage 2 A

Radiation therapy: Intracavitary radiation combined with external-beam pelvic irradiation. Radiation to para-aortic nodes may be indicated in primary tumors 4 centimeters

or larger

Radical hysterectomy and pelvic lymphadenectomy

Stage 2B

Radiation therapy plus chemotherapy: Intracavitary radiation and external-beam pelvic irradiation combined with cisplatin or cisplatin/fluorouracil

Stage III

Radiation therapy plus chemotherapy: Intracavitary radiation and external-beam pelvic irradiation combined with cisplatin or cisplatin/fluorouracil

Stage IV

Radiation therapy plus chemotherapy: Intracavitary radiation and external-beam pelvic irradiation combined with cisplatin or cisplatin/fluorouracil.

2. BACKGROUND

Cancer cervix is the most common type of cancer in Indian women and can cause significant morbidity and mortality. With the wide spread use of screening programs the incidence of advanced carcinoma in reduced, though we still could find large number of patients are being referred to tertiary medical care facility with advanced lesions.

One of the acknowledged treatment options for fairly advanced ca cervix beyond stage II A is radiotherapy (external beam as well as intracavity radiation).

We see lot of patients being referred to medical gastroenterology department of Government General Hospital, Park Town Chennai with symptoms suggestive of radiation induced proctocolitis.

Though the diagnosis of radiation induced proctocolitis is fairly easy and straight forward, the treatment is often elusive leaving the patients with considerable morbidity and reduced quality of life.

The most important issue is the risk of malignancy in the radiated tissues of rectum and sigmiod colon which appears to be substantial.

We undertook this study to identify the risk factors (patients factors, disease factors, treatment regimen factors) for severity of bowel lesions. Also we tried to correlate clinically

the risk of severe RPC to endoscopic severity. The biopsy specimen which was taken in suspicious sites were analysed for evidence of malignancy and to rule out other causes of rectal involvement.

3. AIM OF THE STUDY

1. Identification of risk factors in severe radiation induced proctocolitis in patients treated for advanced Ca cervix by radiotherapy.

2. To correlate the identified risk factors with that of endoscopic severity.

3. To find out the occurrence of adenocarcinoma of rectum and distal large bowel in patients who has radiation proctocolitis.

4. MATERIALS AND METHODS

We retrospectively analysed 73 patients who presented with rectal bleeding along with other symptoms at least six weeks after radiotherapy for Ca Cervix.

Study type Retrospective analytical study

Study period June 2003 to July 2005 (25 months)

Venue Government General Hospital, Chennai

PROTOCOL

Inclusion criteria

Patients with Ca cervix who had radiotherapy (external , Internal or both) presenting after 6 weeks with following symptoms

Rectal bleed

Mucus diarrhea

Tenesmus

Lower abdominal pain

Constipation

Exclusion criteria

Patients presenting less than 6 weeks with above symptoms Infectious diarrhea (as ruled out by stool examination and culture).

Intrinsic diseases of ano-rectum and sigmoid colon including hemorrhoids, fissure in ano, solitary rectal ulcer, IBD and malignancy (by colonoscopy and HPE).

All the patients were admitted . Complete history including co morbid illness and thorough physical examination were done in all patients Routine blood, urine, motion examination, ECG, CXR, USG abdomen were done.

Once stabilized elective colonoscopy was done in all. Colonoscopy was done with Pentax fibro optic colonoscope.

Bowel preparation was done as follows Clear liquids, tender coconut water and soft drinks were permitted the previous day (24 hours). Two tablets of bisacodyl were given the previous night. On the day of the procedure one sachet of PEGLEC was mixed with two litres of water and taken in sips for two hours.

Colonoscopy was done by experienced endoscopists and findings recorded. Biopsy was taken if found necessary.

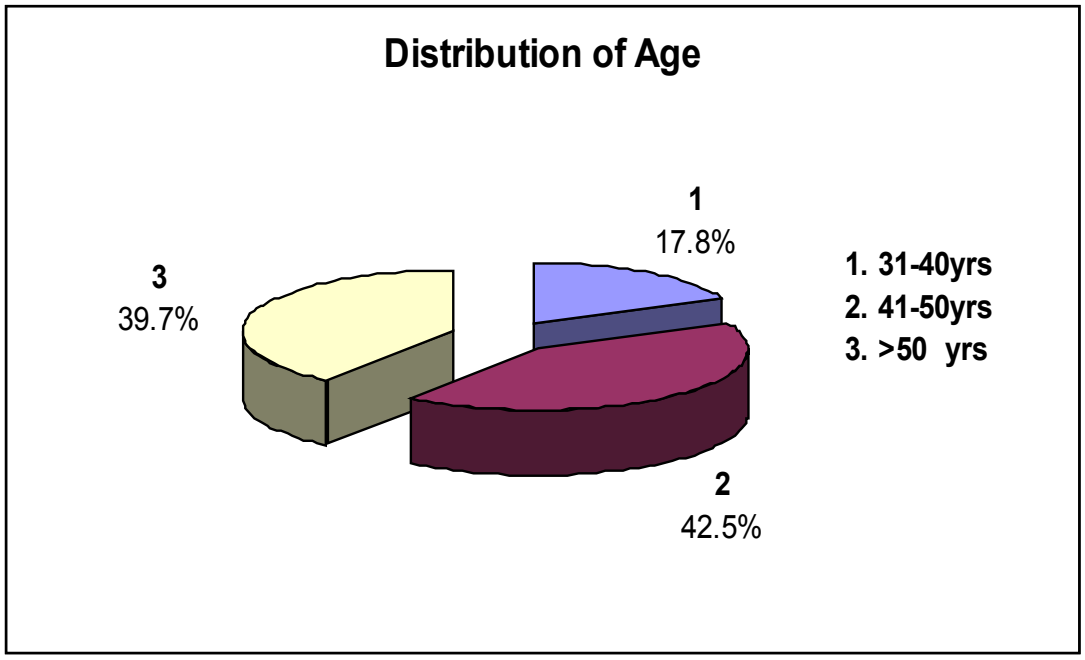
5. RESULTS

Total patients - 73

All are females

Age distribution

39.7% of cases belonged to age group of more than 50 years while 13% were between 31 – 40 years.



Symptoms

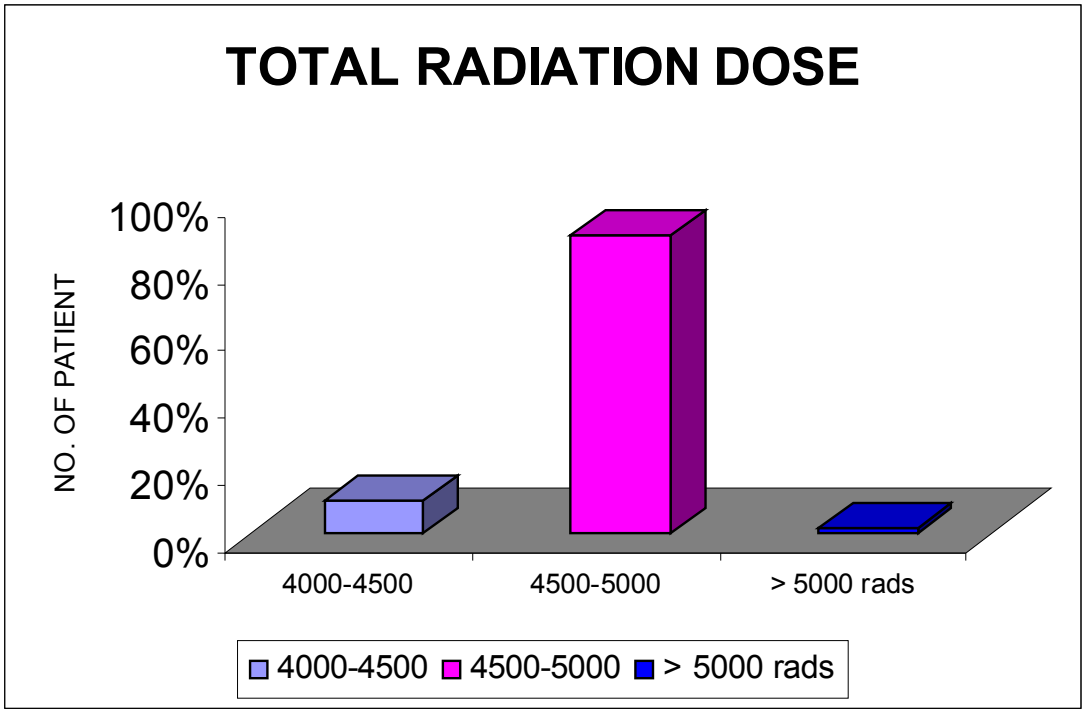
It is noted that the predominant symptom was bleeding per rectum (100%), tenesmus (1.4%) mucus diarrhea (2%), constipation (4.1%), pain abdomen (13.5%) were also seen in increasing frequency.

Comorbid illness

Various comorbid illness were noted in these patients who had radiotherapy. The break up was as follows. Diabetes was seen in 10 cases, atherosclerotic disease in 2 cases , obesity in 2 cases.

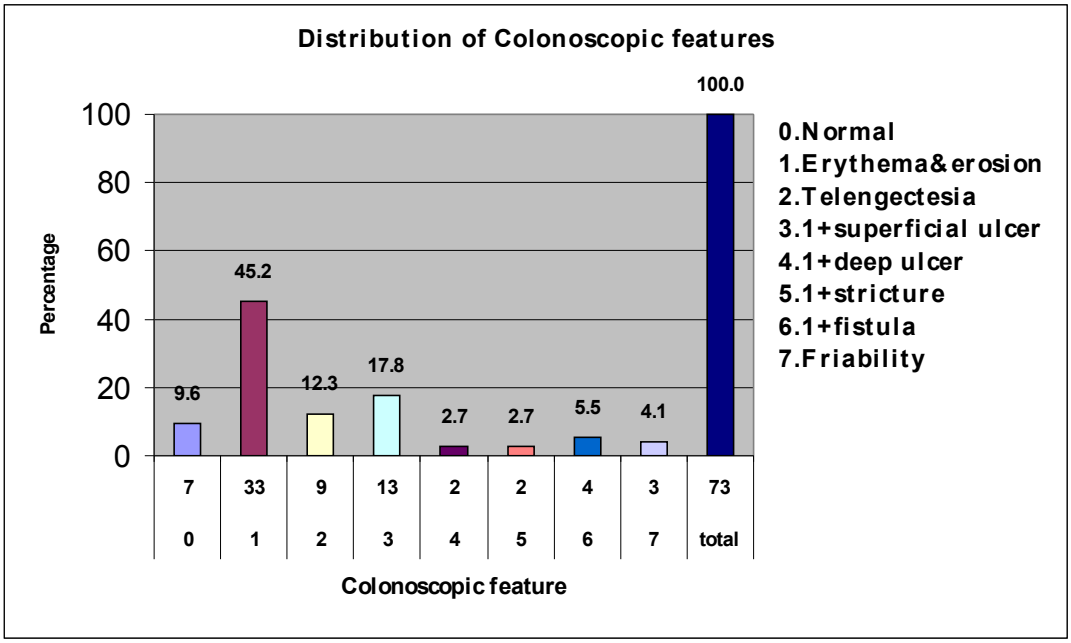
Radiation dose

Most patients who received radiation come in middle radiation dosage (4500 rads to 5000 rads) (89%). Only one patient exceeded dose of 5000 rads (1 case).



Colonoscopy findings

Most common lesion identified was erythema and erosion which comprised of 45.2%. other findings included telengectasia (12.5%), superficial ulcers 17.8%, deep ulcers 2.7%, friability in 4.1%, stricture in 2 cases and fistula in 4 cases (5.5%).



Biopsy and histopathology

Biopsy was done in all cases. All the specimen had significant findings. The common findings in HPE are as follows.

Mucosal ulceration 45%

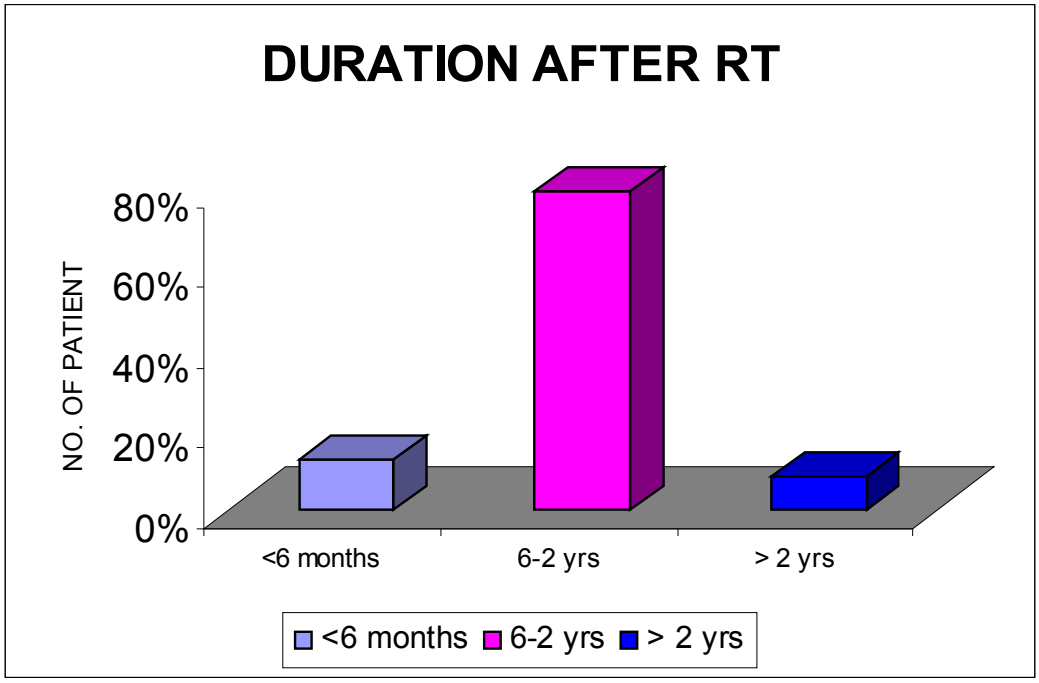
Submucosal fibrosis 23%

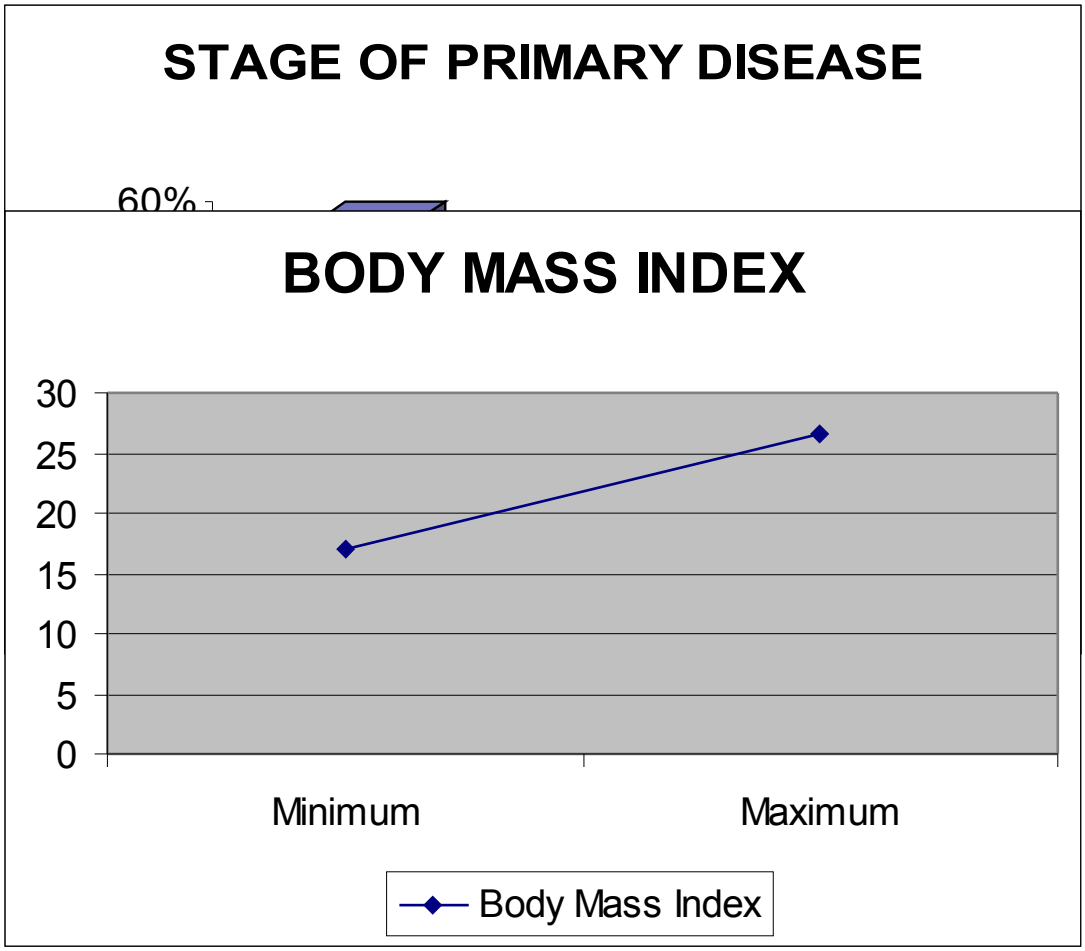
Cellular infiltration 45%

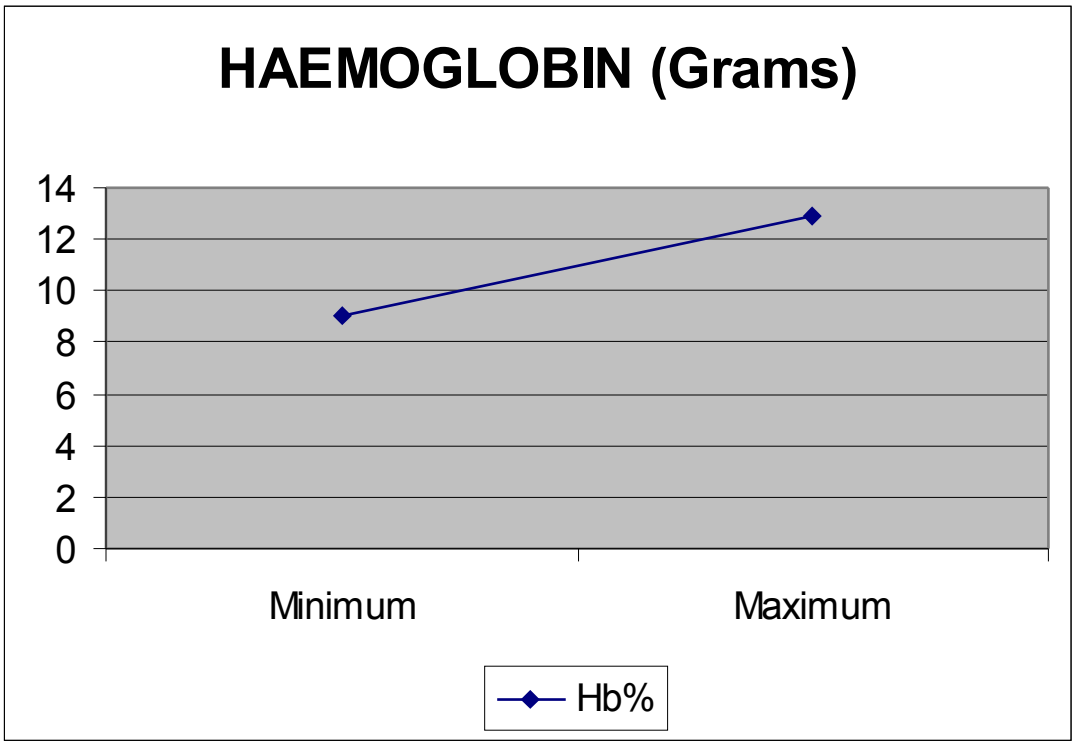
Obliteration of vessels in submucosa 25%

Malignancy

After careful histopthology examination of the samples no dysplasia or malignant changes were noted (0%).






HAEMOGLOBIN (Grams)
14
12
10
8
6
4
2
0
Minimum
Maximum
Hb%

6. DISCUSSION

We analysed 73 patients with radiation induced mucosal damage and tried to identify the risk factors in the causation.

Age correlated significantly with the severity of symptoms. Patients who fall in the third group > 50 years have high incidence of severe symptoms. But it did not have significant implication on the extent of lesion or the colonoscopic severity.

Duration of symptoms is also an important factor identified. Those patients who are symptomatic for > 2 years have severe lesions on colonoscopy. This finding may be attributed to spontaneous healing within 6 months in milder forms of injury as described by various authors.

Gehrig J et al in his study has shown that age and mean duration of illness strongly predicted severe damage[34]. Williams HRT et al has also shown similar results but in his study presence and severity of rectal bleeding was the best predictor.

Total radiation dose when exceeded 5000 rads caused severe disease. It has good correlation with the extent of lesion, severity of lesion by colonoscopy.

Clark BG,Souhami L et has shown that the total radiation dose and the reference point from rectal reference point (arbitrary point which recieves maximum radiation exposure) influences the patient outcomes. Similar study by Dinakaran et al also confided with the same findings.

Intracavity radiation (brachytherapy) correlates well with extent of lesion[35]. More proximity to sigmoid and less protection to the mucosa may be implicated as the causative factor. Yalman D et al in his article has described that intracavity radiation accounted for more extensive disease and more morbidity.

Low BMI when combined with atherosclerotic disease causes severe lesions and more extensive lesion.

Diabetes and low Hb% in the setting of brachytherapy cause extensive damage and fistulization.

This finding confides with various authors but Gehrig J, Hacki WH did not find any correlation with co-morbid illness like diabetes and hypertension. BMI was however influential in determining the extent of illness.

Stage of the disease is also linked to severe disease probably because increased usage of brachytherapy was seen in this subset. Patients having III b disease when having diabetes and atherosclerotic disease with brachytherapy have long duration of symptoms, fistulizing disease, strictures, and more than 12 cm lesion.

In our analysis of 73 patients biopsy was taken in 20 when the lesions have increased friability, nodularity and fistulization. None of the biopsy had any dysplasia or malignant cancer. Probably long term follow may be necessary for identification of dysplasia and malignancy.

Risio M, Coverlizza S et al have postulated that Late cytokinetic abnormalities in irradiated mucosa is a strong predictor of future carcinogenesis though the exact incidence of malignancy occuring in irradiated mucosa appears to be extremely low[36].

Definitive indication favouring surveillance programs post radiotherapy cannot be advised at this stage.

7. CONCLUSION

After the completion of the study the following facts were conceded.

1. The incidence and severity of radiation induced damage to colonic mucosa was influenced by patient factors : age, presence of co-morbidities, low BMI, anemia, long duration of symptoms, disease factors :stage III b disease, treatment factors : total radiation dose, brachytherapy.

2. The clinical assessment of patients with the above risk factors is strong predictor of severe lesions at colonoscopy

3. The risk of malignancy after radiation therapy in the affected colonic mucosa in extremely rare and routine surveillance for the detection of the same is not required.

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