Pre-operative radiotherapy may induce radiation colitis and tumour regression. Histological evaluation of radiation colitis needs to be reproducible to assess disease progression. The severity of radiation colitis can be assessed and graded according to its histological features. Increased severity of disease appears to be associated with a higher degree of cellular atypia and a lesser eosinophilic infiltrate. The severity of histological changes does not appear to be associated with post-operative complications. Tumour regression is an interesting phenomenon, the histological grading of which is of prognostic importance. Patients treated with long course radiotherapy appear to have more incidences of post-operative complications. However, these are thought to be related to the degree of tumour regression rather than to the type of radiotherapy.

Key words: Colitis, Radiation, Radiotherapy, Regression.

INTRODUCTION

Radiation bowel disease is a condition characterized by injury of the bowel mucosa after irradiating neoplastic tissue in pelvic organs. It has been estimated that up to 50% of all solid malignant tumours will receive radiation therapy for curative or palliative purposes. In the UK alone, 12,000 individuals are treated with radical radiotherapy for pelvic cancer annually, and it is estimated that up to 20% of patients who have irradiation to the pelvis will suffer from radiation damage.

SUSCEPTIBILITY

Factors that influence the occurrence and severity of radiation-induced enteritis are either related to treatment or to the host. Factors that are related to treatment:

1) Dose: The higher the dose of radiotherapy the more the toxicity.

2) Field: The larger the field of radiotherapy the more the toxicity.

3) Post-operative radiotherapy is more toxic than pre-operative radiotherapy. In the Uppsala rectal cancer trial in which patients were randomized to receive either preoperative or postoperative radiotherapy, there was marked difference in toxicity between the two regimens.

In this study, all patients who had preoperative treatment experienced no or minimal radiation-related morbidity and there was no measurable excess of post-operative mortality. In contrast, amongst those allocated to post-operative radiotherapy, over 90% experienced radiation-related complications.

4) Concomitant chemotherapy also increases the risk of toxicity.

Factors related to the host include diabetes, atherosclerosis and smoking. It is suggested that these factors enhance vascular damage and increase the effect of radiation damage.

PATHOGENESIS

While radiation targets the neoplastic cells, the radiation field often includes non-neoplastic tissue. The aim of the radiation is to stop the cell proliferating cycle with most of the damage to the nucleus happens when the cell is in G2 than in G1 and S phases.

The radiation energy causes its effect by both direct and indirect mechanisms. The direct damage is on the DNA by breaking the single or double chromosomal strands, while the indirect damage is by ionization of the cellular water leading to formation of free radicals, which lyse the nuclear and cellular membranes. These mechanisms lead to the morphological changes, which are characteristic of acute radiation bowel disease. Rapidly dividing cells are therefore more radiosensitive than slowly dividing ones because they go more frequently through the mitotic cycles and slowly proliferating tissues show their signs of damage months or years after exposure. In the gut, for ex-
ample, vascular tissue has a slower turnover rate than the epithelial lining but has a faster rate than fibrous tissue. The additional predisposing factors for radiation-induced intestinal injury in the gut include hypertension, coincident chemotherapy and prior surgery.\textsuperscript{10}

**CLINICAL FEATURES**

Broadly speaking the clinical features of radiation-induced intestinal injury present themselves in two phases:

The acute phase starts during or immediately after the treatment in about 80% of the patients and is manifested by crampy abdominal pain, tenesmus and watery diarrhoea. The symptoms usually get better within 3 months after finishing treatment and symptoms that persist or arise subsequently after that time are deemed to be late toxic effects.\textsuperscript{4}

The chronic phase ranges from chronic gastrointestinal symptoms such as bleeding, diarrhoea, malabsorption, vomiting, abdominal distention and abdominal pain which can occur in up to 50% of patients, to more severe morbidity or life-threatening complications that include fistulation, sepsis, stenosis, intestinal failure, perforation and bleeding (4-8% after 5-10 years).\textsuperscript{12}

Some authors have specified a latent phase, which appears after several years or decades due to abnormalities in the DNA. This may lead eventually to mutations and carcinogenesis.\textsuperscript{13}

**PATHOLOGY**

Morphology of the non-tumorous gut:

One of the first articles, which appeared on the topic, was the article from our group.\textsuperscript{14} This study followed the progress of the disease in a cohort of patients by sequential light and electron microscopic examination of rectal biopsies and has shown that morphologically the disease can be divided into three phases with three predominant patterns of cell injury. The first or acute phase is purely epithelial and characterised by megalonucleosis, abnormal mitotic figures and eosinophilic infiltrate in the lamina propria with formation of eosinophilic crypt abscesses. The nuclei are so bizarre that for the unwary pathologist it may lead to the over-diagnosis of dysplasia. These features have been confirmed by Leupin et al.\textsuperscript{15} They have shown that most of the morphological characters appear in short course therapy such as severe mucosal inflammation, prominent eosinophils, crypt disarray, crypt epithelial damage, nuclear abnormality and apoptosis of the crypt epithelium while the long course radiotherapy show either none or very rarely detected features.

The second phase appears weeks or months later and is also called the vascular phase and is characterised histologically by narrowing of the vessels by subendothelial oedema and fibrin deposition. On electron microscopy there is endothelial cell necrosis and platelet thrombus formation. We believe this his is a progressive phenomenon and will lead to severe fibrosis, which is a characteristic of the third phase of the disease. The next phase is the late (stromal/fibrous) phase, which appears months or years later and is characterised by the stromal (fibrous) component, which shows severe stromal fibrosis. There is usually dense fibrosis of the lamina propria and the wall with decrease number of inflammatory cell infiltrates.

In a study by Carr et al. from South Manchester when vessels from colectomy specimens were examined after been perfused with barium sulphate suspension, they

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**TABLE 1**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
<th>Degree of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Eosinophilic infiltration</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic infiltration crypt abscesses</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Cellular atypia</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>Surface epithelial erosion</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic infiltration</td>
<td>+</td>
</tr>
<tr>
<td>Moderate</td>
<td>Eosinophilic infiltration crypt abscesses</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Cellular atypia</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Surface epithelial erosion</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic infiltration</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic infiltration crypt abscesses</td>
<td>+</td>
</tr>
<tr>
<td>Severe</td>
<td>Eosinophilic infiltration crypt abscesses</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Cellular atypia</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Surface epithelial erosion</td>
<td>+++</td>
</tr>
</tbody>
</table>

+++ = severe; ++ = moderate; + = mild; +/- not seen or very mild

**TABLE 2**

<table>
<thead>
<tr>
<th>Five-point TRG</th>
<th>Description</th>
<th>Three-point TRG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No viable cancer cells</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Single cells or small groups of cancer cells</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Residual cancer outgrown by Fibrosis</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Significant fibrosis outgrown by cancer</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>No fibrosis with extensive residual cancer</td>
<td>5</td>
</tr>
</tbody>
</table>
showed that in chronic radiation bowel disease vascular pattern is significantly deranged. Indeed, in severe cases, they demonstrated that large segments of the bowel are devoid from normal vasculature and these segments are liable to stenosis, ischaemia and perforation.

It is important to realise that the epithelial damage in the late phase disease can show crypt distortion similar to inflammatary bowel disease and therefore it is very important for the pathologist to have the clinical picture before making such a diagnosis.

Histological grading of radiation colitis:

Pre-operative radiotherapy is known to induce radiation colitis in the non-neoplastic epithelial tissue.

We have previously graded the degree of radiation colitis into mild, moderate and severe (Table 1) and demonstrated that post-operative abdominal complications are not linked to the grade of radiation damage and have shown that acute damage is more common in short course radiotherapy. However, in this study we have shown that postoperative complications are more common in short course radiotherapy. Despite acute severe inflammation, in several other studies, none of the patients treated by short-term irradiation developed peri-operative complications. Most of the studies have also demonstrated that complications are not related to the type of radiotherapy. More recently we have studied 75 patients of rectal cancer who had pre-operative radiotherapy for locally advanced disease (in Press) and reinforced the view that short course of radiotherapy induces severe radiation colitis but demonstrated no relationship between grading of radiation colitis and postoperative complications. We have also found that the post-operative complications are higher in patients receiving long course radiotherapy. We concluded that this finding might be due to the degree of histological tumour regression in these patients rather than the type of radiation (regressed tumours showed higher incidence of post-operative complications).

B- Morphology of the tumour cells:

One exciting phenomenon is tumour regression in response to pre-operative radiotherapy given for rectal cancer patients. In 1991, James et al. published their paper on prognostic factors in colorectal cancer treated by preoperative radiotherapy and immediate surgery and showed that radiation over grades and understages the disease leading to tumour regression.

During the last decade neo-adjuvant therapy has become the standard treatment of locally advanced rectal cancer aiming to downstage the tumor, decrease local recurrence rate and improve survival of patients. Neo-adjuvant therapy often produces morphological changes in tumour characteristics as well as causing a reduction in tumour volume. The tumour regression grade, which has been shown to be a prognosticator of favorable outcome, after cancer radiotherapy was initially proposed by Mandard in 1994 and was based on oesophageal cancer using the 5 point regression scoring system.

Later, many authors applied the same principles on rectal cancer with many grading systems followed ranging from 3 to 5 points grading systems (Table 2).

Regression changes in tumour cells include cancer cells showing cytoplasmic vaculization and/or eosinophilia, nuclear pyknosis, and necrosis. The stromal changes included fibrosis and oedema, with or without inflammatory infiltrate with giant cells and calcification. The overall regression grade is determined by the amount of viable tumour cells versus fibrosis.

CONCLUSIONS:

Pre-operative radiotherapy may induce radiation colitis and the severity of radiation colitis can be assessed and graded into mild, moderate and severe. Increased severity of disease appears to be associated with a higher degree of cellular atypia and a lesser eosinophilic infiltrate. There was no trend in the development of complications with the radiation colitis grade or the type of radiotherapy in general. More abdominal complications are seen in long course radiotherapy and this is due to the degree of tumour regression rather than the type of radiotherapy used. Radiotherapy can produce tumour regression which can also be graded and this is shown to be a prognosticator of favourable outcome and related to the development of postoperative complications.

CONFLICT OF INTEREST: None.  

SUMMARY

RADIJACIONA POVREDA CREVA I KLINIČKE IMPLIKACIJE


Ključne reči: kolitis, radiacija, radiotherapija, regresija

REFERENCES:


