Early Intestinal Changes Following Abdominal Radiotherapy
Comparison of Endpoints

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Purpose: To compare tests for intestinal function with clinical scores after abdominal irradiation.

Patients and Methods: At the Department of Radiotherapy, Erfurt, Germany, intestinal changes were studied in 91 patients receiving abdominal radiotherapy between 1992 and 1996. Conventional fractionation (1.8–2 Gy per fraction, total doses 30.6–62.5 Gy) was applied. Before and at weekly intervals during radiotherapy, the clinical response was scored according to RTOG/EORTC for the upper and lower gastrointestinal (GI) tract. Resorption tests for vitamin B₁₂ and D-xylose were performed before the onset and immediately after treatment.

Results: The clinical response displayed a well-defined dose-effect relationship with grade 1 effects in 5% and 50% of the patients at about 10 Gy and 50 Gy, respectively. For grade 2 reactions, 5% and 50%-effective doses were 20–30 Gy and 60–80 Gy. Effects in the upper and lower GI tract were highly correlated. Changes in body weight did not show a correlation with other clinical symptoms. Changes in resorption also displayed a significant dose effect. However, no correlation was found with the clinical symptoms in the individual patient.

Conclusion: In the present study, the clinical manifestation of intestinal side effects according to RTOG/EORTC criteria was reflected by neither the vitamin B₁₂ nor by the D-xylose resorption test. Hence, these tests cannot be regarded as useful for objective quantitation of intestinal radiation injury.

Key Words: Abdominal radiotherapy · Radiation sequelae · Intestine · Resorption assays
Introduction

Physical developments in radiation oncology, such as the introduction of high-energy photons, multiple-field treatments, or intensity-modulated irradiation, allow for positioning of the high dose volume at almost any location within the body. However, these modern irradiation techniques are also associated with changes in dose distribution in normal tissues. The volume of normal tissues exposed to high doses can be significantly reduced, e.g., for the intestine or the bladder during pelvic irradiation \[6, 13\], in order to exploit the known volume effect for these organs (e.g., \[3, 4, 10, 18, 19, 25, 33\]). Usually, this decrease in the normal tissue volume exposed to high doses is accompanied by an increase in the low dose volume. This has led to significant changes in the pattern of clinical manifestations of normal tissue morbidity. While severe structural effects, like fistula or ulcerations, are rare, changes in organ and tissue function have become the dominating parameter of normal tissue effects of radiation therapy.

Moreover, developments in diagnostic methods allow for objective and quantitative assessment of a variety of radiation-induced changes in both function and morphology of normal tissues and organs. However, detailed clinical data on the dose effect in radiotherapy, particularly using modern diagnostic endpoints for objective assessment, are scarce for the majority of tissues.

The intestine is one of the critical organs in abdominal radiotherapy. Early epithelial destruction is accompanied by submucosal changes, with vasodilatation and edema. The consequences are persisting edema, an increase in perivascular fibers, intimal hyperplasia, and vessel wall hyalinosis. The consequent insufficiency in the supply of the mucosa with blood and nutrients results in epithelial atrophy \[2, 9, 12, 26, 31, 32\]. Eventually, fibrotic changes in the submucosa, accompanied by vascular occlusions, are seen. In contrast to the colon, where colitis cystica profunda is a frequent observation, these changes are rare in the small intestine. Late ulcerations develop on the basis of secondary traumata (feces, pancreatic enzymes, chemotherapy). The intensity of early effects, both severity and duration, significantly impact on the risk for the development of late changes, indicating a strong consequential component \[7, 8\]. Early as well as late mucosal changes result in an impairment of the digestive and absorptive functions of the intestine, which manifest as various forms of malabsorption, with acute or chronic diarrhea \[5, 34\].

A variety of approaches for amelioration of intestinal side effects of radiotherapy have been tested \[35, 36\]; while most of these focused on large bowel and rectum \[16, 17, 26\], data for the small intestine are scarce \[30\].

Despite the fact that the intestinal response has qualitatively been studied in much detail, data on the effect of radiation dose in the human intestine are scarce. Moreover, objective assays for the quantitation of the response still have to be established. These, however, are a major prerequisite for objective evaluation of novel supportive care approaches.

The present investigation was initiated in order to study the intestinal radiation response to abdominal radiotherapy in a prospective investigation. The clinical response was documented in detail. For the determination of functional changes, resorption assays for vitamin B\textsubscript{12} and D-xylose were performed.

Patients and Methods

From 10/1992 to 03/1996, 91 patients, treated with abdominal radiotherapy at the Department of Radiotherapy, Klinikum Erfurt GmbH, Germany, were included in this study. The patients’ age ranged from 18 to 74 years. The diagnoses were lymphogranulomatosis (n = 22), non-Hodgkin’s lymphoma (NHL, n = 13), gastric NHL (n = 4), seminoma (n = 45), carcinoma of the kidney (right: n = 4, left: n = 2), and rhabdomyosarcoma (n = 1). The patients have been characterized in detail elsewhere \[14\].

In 72 of these patients, three-dimensional (3-D) treatment planning was performed. In the remaining 19 patients CT-based planning was applied in three planes. For this, CTs were carried out in the treatment position and included the target volume plus 2 cm cranially and caudally. The mean total dose (100% isodose) ranged from 30.6 to 62.5 Gy, depending on the target volume. The dose per fraction was 1.8–2.0 Gy, given five times per week. Patients were grouped according to the planning target volumes and corresponding doses as summarized in Table 1.

It must be emphasized that the heterogeneity of doses and treatment volumes was a prerequisite to observe a wide range of grades of radiation-induced changes.

Diagnostic Procedures and Endpoints

Examinations for intestinal changes were performed before, during and im-

<table>
<thead>
<tr>
<th>Group</th>
<th>Target volume</th>
<th>Dose* (Gy)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Paraortic lymph nodes</td>
<td>36.8 ± 3.8</td>
<td>44\textsuperscript{a}</td>
</tr>
<tr>
<td>B</td>
<td>Paraortic lymph nodes plus spleen</td>
<td>30.6 ± 5.7</td>
<td>10</td>
</tr>
<tr>
<td>C</td>
<td>Paraortic lymph nodes plus right renal bed</td>
<td>62.5 ± 0.0</td>
<td>4</td>
</tr>
<tr>
<td>D</td>
<td>Paraortic lymph nodes plus left renal bed</td>
<td>62.3 ± 0.3</td>
<td>3</td>
</tr>
<tr>
<td>E</td>
<td>Paraortic, iliac and inguinal lymph nodes</td>
<td>35.6 ± 6.2</td>
<td>14\textsuperscript{c}</td>
</tr>
<tr>
<td>F</td>
<td>Paraortic, iliac, inguinal lymph nodes plus spleen</td>
<td>33.2 ± 7.5</td>
<td>11</td>
</tr>
<tr>
<td>G</td>
<td>Gastric region, mesenteric root inguinal lymph nodes</td>
<td>40.7 ± 4.1</td>
<td>5</td>
</tr>
</tbody>
</table>

\*radiation dose at 100% isodose, with standard deviation; \textsuperscript{a}one patient including irradiation of pedicle of the spleen; \textsuperscript{c}two patients including irradiation of pedicle of the spleen