Radiotherapy and Oncology 123 (2017) 147–153

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Inflammatory bowel disease

# Acute toxicity and surgical complications after preoperative (chemo) radiation therapy for rectal cancer in patients with inflammatory bowel disease

Steven L. Bosch [a,*,1], Stefan J. van Rooijen [b,1], Guus M.J. Bökkerink [b], Hidde J.W. Braam [b], Lauranne A.A.P. Derikx [c], Philip Poortmans [d], Corrie A.M. Marijnen [e], Iris D. Nagtegaal [a], Johannes H.W. de Wilt [b]

[a] Department of Pathology; [b] Department of Surgery; [c] Department of Gastroenterology and Hepatology; [d] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen; and [e] Department of Radiation Oncology, Leiden University Medical Center, The Netherlands

ARTICLE INFO

*Article history:*
Received 16 December 2016
Received in revised form 16 February 2017
Accepted 19 February 2017
Available online 10 March 2017

*Keywords:*
Inflammatory bowel disease
Rectal cancer
Preoperative therapy
Chemoradiation therapy
Short course radiation therapy

ABSTRACT

*Purpose:* Preoperative therapy reduces local recurrences and may facilitate surgery in rectal cancer patients. However, in patients with inflammatory bowel disease (IBD) this treatment is often withheld due to the perceived risk of excessive side-effects, even though evidence is limited. The purpose of this study is to investigate the effects of preoperative therapy on acute toxicity and post-operative complications in IBD patients with rectal cancer.

*Methods:* The Dutch pathology registry (PALGA) was searched for patients with IBD and rectal cancer treated between January 1991 and May 2010. Histopathology and clinical charts were reviewed to confirm IBD diagnosis and evaluate clinical and pathological characteristics.

*Results:* Out of 161 patients, 66 received preoperative therapy (41%), including short-course radiation therapy (SC-RT), long course radiation therapy (LC-RT), and chemoradiation therapy (CRT) in 32, 13, and 21 patients respectively. Grade $\geq 3$ acute toxicity occurred in 0 patients (0.0%), 1 patient (7.7%), and 6 patients (28.6%) respectively ($p = 0.004$). Systemic corticosteroids were used by 10.5% of patients at time of treatment. Grade $\geq 3$ post-operative 30-day complication rate (28.1% overall) was not associated with type of preoperative therapy.

*Conclusion:* Results did not show excessive rates of toxicity or post-operative complications and support the use of standard preoperative therapies for rectal cancer (especially SC-RT) in IBD patients with relatively indolent disease. Caution is warranted in patients with active IBD, since the exact impact of active bowel inflammation could not be determined retrospectively. Prospective studies should investigate the influence of active IBD on acute and late toxicity in patients receiving pelvic irradiation.



Inflammatory bowel disease (IBD), including ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis (IC), is a chronic, idiopathic and immunologically mediated inflammatory disorder of the gastrointestinal (GI) tract characterized by episodes of exacerbations and remissions [1]. Patients with IBD have an elevated risk of developing colorectal cancer through the inflammation-dysplasia-carcinoma pathway. The risk increases markedly with disease duration and extent, although modern management has been effective in decreasing the colorectal cancer incidence to levels not much higher than in the general population [2–8]. However, colorectal cancer remains a significant problem in IBD patients, with worse stage-specific survival rates compared with colorectal cancer in patients without IBD [9].

For IBD patients who develop cancer in the rectum, optimal treatment strategies remain unclear. Standard preoperative therapy regimes, such as chemoradiation therapy (CRT) for locally advanced rectal cancer or short course radiation therapy (SC-RT), sometimes used for non-advanced tumors or in frail patients, are often withheld in patients with IBD, due to the perceived risk of excessive levels of side-effects [10–12]. A review on radiotherapy for cancer in IBD patients concluded that external beam radiotherapy (EBRT) produced a moderate increase in acute and late toxicity in IBD compared with non-IBD patients, whereas toxicity levels after brachytherapy for prostate cancer were similar [13]. However, this review included tumors in various locations treated with

* Corresponding author at: Dept. of Pathology 824, Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands.
*E-mail address:* Steven.Bosch@radboudumc.nl (S.L. Bosch).

[1] SB and SvR contributed equally to the study.

http://dx.doi.org/10.1016/j.radonc.2017.02.009
0167-8140/

either pelvic or abdominal irradiation. Previous studies specifically investigating the effects of radiation therapy in IBD related rectal cancer showed conflicting results, and are restricted by limited patient numbers treated over an extended period of time in which imaging and radiation techniques, as well as (peri-)operative management have evolved substantially [14,15].

The current study therefore aims to investigate the risk of both acute RT induced toxicity and 30-day post-operative complications in IBD patients with rectal cancer undergoing preoperative (chemo)radiation therapy. Results may guide and optimize current rectal cancer treatment strategies for patients with IBD.

## Methods

### *Patient selection*

We searched PALGA, the nationwide network and registry of histopathology and cytopathology in the Netherlands, to identify patients with a history of IBD who were diagnosed with rectal cancer between January 1991 and May 2010. PALGA collects histopathological and cytopathological diagnoses generated in the Netherlands since 1971 and has complete national coverage since 1991 [16]. Approval of the PALGA Privacy Commission and Scientific Council as well as the Radboudumc institutional ethics committee was obtained (registration number 2012/030). A search was performed using the search terms: *"rectal cancer"* and/or *"rectosigmoid cancer"* combined with *"ulcerative colitis"*, *"Crohn's disease"*, and/or *"indeterminate colitis"* as well as several related terms including *"ileitis"*, *"ulceration"*, *"ulcer"*, *"inflammation"*.

The search yielded records of all patients with a history of rectal/rectosigmoid cancer combined with at least one pathology report of IBD or non-specific bowel inflammation. Records were manually scrutinized by two investigators (SB and IN) to select patients who were suspected to have a genuine IBD diagnosis. Of the selected patients, histopathological slides of diagnostic IBD biopsies and rectal resection specimens containing the primary tumor (or tumor biopsy if a resection was unavailable) were obtained and reviewed to confirm both the IBD and rectal cancer diagnoses and document tumor characteristics. In addition, medical charts were searched to extract clinical data.

### *Inclusion and exclusion criteria*

Only patients with available clinical data after medical chart review were included in the analysis. Patients were excluded if the IBD diagnosis could not be confirmed after review of pathology data and clinical charts, or when IBD was diagnosed after treatment for rectal cancer. Likewise, patients who did not have a rectal tumor (distal edge >15 cm from the anal verge) were excluded. In addition, cases were excluded in case of an administrative mismatch, incorrectly linking records from a patient with IBD to another patient with rectal cancer who had a similar last name and birth date.

### *Clinicopathological characteristics*

All clinical and treatment characteristics were retrieved retrospectively from the medical charts. Pathological characteristics were determined retrospectively by centrally reviewing the original histopathological slides and pathology reports. Extracted clinical data included sex, date of birth, presence of comorbidities, type of IBD, date of IBD diagnosis, disease duration, date of rectal cancer diagnosis, presence of distant metastases, type of preoperative treatment (if any), use of corticosteroids at time of treatment, therapy-induced acute toxicity/adverse events, type of surgery, and 30-day post-operative complications.

IBD diagnosis was specified as UC, CD or IC based on clinical, histopathological and endoscopic characteristics. Preoperative radiation therapy consisted of EBRT using a three-dimensional conformal technique or intensity-modulated radiotherapy (IMRT). From 2001 onwards the prevailing guidelines recommended that the clinical target volume should include the primary tumor and the mesorectum with vascular supply, containing the perirectal, presacral and internal iliac nodes. The recommended upper border was at the level of the promontory. The perineum was included if an abdominoperineal excision (APE) was planned, whereas the lower border was 3 cm above the anal verge if the planned operation was a low anterior resection (LAR [17]. SC-RT was defined as $5 \times 5$ Gy given over a 5–7 day period [18]. LC-RT treated patients received preoperative radiation with 45–50 Gy given in 25–28 fractions of 1.8–2.0 Gy. In the CRT group concurrent fluoropyrimidine based chemotherapy was added to the long-course radiation schedule [11,19,20].

Acute toxicity (occurring during preoperative therapy) was graded according to the National Cancer Institute Common Terminology Criteria (version 4.0) [21]. In patients who underwent radical surgery, 30-day post-operative complications were graded using the modified Clavien-Dindo classification [22]. Comorbidities were scored according to the Charlson comorbidity index (CCI) [23]. Tumor related histopathological characteristics were scored in patients who underwent a resection of the rectum. This included TNM-stage [24], circumferential margin (CRM) involvement (tumor cells at a distance of $\leq$1 mm from the CRM), and histopathological type/differentiation grade [25].

### *Statistical analysis*

All data were entered in a database and analyzed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Categorical variables were analyzed using the $\chi^2$ test. For non-parametrical continuous variables the Mann–Whitney U test or independent samples Kruskal–Wallis test was used were appropriate. A $p$-value of <0.05 was considered statistically significant whereas a $p$-value of <0.1 was interpreted as a trend towards significance.

## Results

### *Patient selection*

The initial PALGA search yielded 2035 potential cases with rectal or rectosigmoid cancer and possible IBD (Fig. 1). The manual search identified 364 patients, treated in 75 hospitals, who were considered likely to be genuine IBD patients with rectal cancer. For reasons of feasibility clinical chart review was limited to 196 patients who underwent surgery in 41 centers, including all centers with at least 4 eligible patients. For the remaining 168 patients either the medical charts were not available in the visited treatment center or the patients were treated in one of the centers with no more than 3 eligible patients. Thirty-five cases were excluded after review of clinical and histopathological data resulting in 161 IBD patients with rectal cancer who were included in the analysis. Reasons for exclusion were: no rectal cancer (tumor >15 cm from the anal verge; $n = 17$ and tumor in a perineal fistula after proctectomy; $n = 1$), unconfirmed IBD diagnosis ($n = 6$), both absence of rectal cancer and unconfirmed IBD diagnosis ($n = 2$), IBD diagnosis following rectal cancer treatment ($n = 3$), and administrative mismatch ($n = 6$).

### *Clinicopathological characteristics*

Table 1 provides clinical and pathological characteristics per treatment group. Out of 161 IBD patients, 83 patients had UC, 69