Scandinavian Journal of Gastroenterology. 2015; 50: 197–203

informa
healthcare

ORIGINAL ARTICLE

Radiotherapy-induced mesorectum alterations: histological evaluation of 90 consecutive cases

LUCA REGGIANI BONETTI[1], FEDERICA DOMATI[2], ALBERTO FARINETTI[3], MARIO MIGALDI[1] & ANTONIO MANENTI[3]

[1]*Department of Forensic Medicine, Laboratory and Pathologic Anatomy, University of Modena and Reggio Emilia, Modena, Italy,* [2]*Department of Medicine and Medical Specialties, University of Modena and Reggio Emilia, Modena, Italy, and* [3]*Department of Surgery, University of Modena and Reggio Emilia, Modena, Italy*

Abstract

Objective. In order to identify the radiotherapy-induced histological modifications in the mesorectum, we reviewed the surgical specimens of 90 rectal resections comprehensive of the total mesorectal excision (23 cases radiologically classified as cT2N0M0 and 67 as cT3N0M0). All patients were preoperative treated with radiotherapy: 20 with 50 Gy, 20 with 20 Gy and 50 Gy irradiation associated to FOLFOX scheme chemotherapy. ***Material and methods.*** Routine hematoxylin and eosin stained serial slides at 5 mm of intervals were obtained from surgical specimens and included the tumor site and the adjacent irradiated mucosa, the submucosa and the muscular layers of the rectal wall and the mesorectal adipose tissue, completely removed until to the mesorectal fascia. Ten subjects (eight cT2N0M0 and two cT3N0M0), who did not received preoperative oncological treatments were adopted as controls. ***Results.*** Histologically, examination revealed fibrosis of the adipose tissue in 86 cases (95%), vascular damage including vasculities and fibrotic thickening wall of arteries and veins in 46 cases (51%), sclero-hyalinosis of lymph nodes with pericapsular fibrosis in 22 cases (23%) and perineural deposition of fibrosis in 12 (13%). These findings were ubiquitously observed in the whole mesorectum. Fibrosis of the adipose tissue and vasculitis were mainly associated to the combination of 50 Gy radiations plus chemotherapy ($p < 0.05$). ***Conclusion.*** The detection of histopathological alterations in the mesorectum can give reason of the well-known postoperative complications and long-term sequels.

Key Words: *mesorectum, radiotherapy, rectal cancer*

Introduction

The main interests of histopathological studies concerning the mesorectum include its involvement by the tumor masses as well as the presence of lymph node metastasis and the impact of its surgical resection on the accuracy of the stadiation of the rectal tumors [1–5]. On the other hand, the relevance of neoajuvant radiotherapy in rectal cancer is well known, as well as the post-treatment complications, early and late clinical sequels [6–8]. The main purpose of our study is to assess histological modifications of the mesorectal anatomical components induced by neoajuvant radiotherapy.

Methods

We reviewed the histological specimens of 90 surgically removed rectum for primary adenocarcinoma, with total mesorectal excision after neoajuvant radiotherapy, alone or in association with chemotherapy. Cases were selected from a Specialized Colorectal Cancer Registry instituted in 1984 in the Province of Modena (Italy) in which clinical and pathological informations about the tumors and its behavior were meticulously scheduled [9,10]. Only tumors preoperatively classified as cT2N0M0 and cT3N0M0 at computed tomography (CT) or magnetic resonance (MR) were included in the study. For cT3 tumors, we

Correspondence: Luca Reggiani Bonetti, MD, PhD, Pathological Anatomy, Policlinico of Modena – University of Modena and Reggio Emilia, Via del Pozzo 71 – 41100 Modena, Italy. Tel: +390594222001. Fax: +390594224998. E-mail: reggiani.luca@policlinico.mo.it

(Received 28 August 2014; revised 15 October 2014; accepted 22 October 2014)

ISSN 0036-5521 print/ISSN 1502-7708 online © 2015 Informa Healthcare
DOI: 10.3109/00365521.2014.983153

considered those with only partial involvement of the mesorectal adipose tissue (within 1 cm of maximum depth) in order to keep out the possible histological alterations associated to neoplastic regression (tumor site) and not induced by radiotherapy. Cases with a preoperative radiological signs of involvement of the mesorectal fascia were excluded.

Based on the different schemes of preoperative oncologic treatments, all 90 cases were subdivided into 4 groups: *group 1* that included 50 subjects (2 cT2N0M0 and 48 cT3N0M0) who received a 50 Gray neoadjuvant radiation in association with chemotherapeutic FOLFOX regimen, 6–8 weeks before surgery; *group 2* that regarded 20 patients (8 cT2N0M0 and 12 cT3N0M0) treated with 50 Gray neoadjuvant radiation alone; *group 3* that concerned 20 patients (13 cT2N0M0 and 7 cT3N0M0) underwent to neoadjuvant radiotherapy of 25 Gray followed by surgery alone within 10 days. Ten subjects (eight cT2N0M0 and two cT3N0M0) who did not receive preoperative oncological treatments were used as control cases – *group 4*.

Slides stained with hematoxylin and eosin, obtained from surgical specimens, fixed in 10% buffered formalin solution for 48 h and representative of the whole tumor with the surrounding complete excised mesorectum, were available for each cases and carefully reviewed. All the specimens were systematically examined through serial sectionings on the transversal side with a 5-mm interval. Slides included the mucosa, submucosa and muscular layers of the rectal wall and the mesorectal adipose tissue, completely removed up to the mesorectal fascia. We examined an average of 44 slides for each case (range 28–52 consecutive slides), following the procedure described by Parfitt and colleagues [1].

The regression of the neoplastic masses was semiquantitatively determined by the amount of viable tumors versus the amount of fibrosis, ranging from no evidence of any treatment effect to a complete response with no more viable tumor identified (Dworak's system) [11]. Residual of the tumor mass was staged using the TNM criteria [12].

The meticulous histological examination of the mesorectum tissue focused on the evaluation of the interstitial tissue, arterial, venous and lymphatic vessels, nerves and lymph nodes.

Statistical analysis

Fisher exact test was applied to compare the categorical variables. A probability (p) value less than 0.05 was considered statistically significant for the statistical analyses. Data were analyzed using the SPSS package version 6.1.3 (SPSS Inc., Chicago, IL, USA).

Ethical issue

The study has been performed according to the Declaration of Helsinki and the study-design has been approved by local ethics committee (RIF. PROTOCOL. N. n 248/13 C.E. – October 29, 2013; *Comitato Etico della Provincia di Modena - Italy*). The patients were collected in anonymous file, and no clinical or personal data were treated in the present study.

Results

Clinical and general histopathological features of the studied cases (90 treated subjects and 10 controls) are listed in Table I. In particular, the average patient's age at the moment of the diagnosis was 67 ± 11,23 years (56–84) and 69 ± 14,18 years (61–78), respectively, in the two groups (cases and controls), with no difference between males (52 subjects) and females (48 subjects). Preoperative MR staging showed 31 cT2N0M0 tumors (23 cases and 8 controls) and 69 cT3N0M0 (67 cases and 2 controls). No tumor regression (Dworak regression grade 0) was observed in 25 cases represented by 23 ypT3NoM0 and 2 ypT2N0M0 tumors; a partial tumor regression (Dworak regression grade 1, grade 2 and grade 3) was observed in 59 cases (16 ypT2N0M0 and 43 ypT3N0M0). Complete tumor regression (Dworak regression grade 4) was graduated in six cases (ypT0N0M0). No metastatic lymph nodes were histologically detected, and all the surgical margins (mucosal and circumferential mesorectal margins) were disease-free.

The mainly histological modifications of the mesorectum induced by preoperative radiotherapy were observed in the adipose tissue, in arterial, venous and lymphatic vessels, in the nerves and lymph nodes and are listed in Table II. The most evident features were dense and compact fibrotic strands connected with the rectal fascia and with radial pattern of growth, dislocated in the interstitial component of the mesorectum. Although diffusely detected in the specimens of 86/90 (95%) treated cases (Figure 1A), they were mainly observed in the *group 1* (50/50 subjects preoperatively treated with combination of 50 Gy plus chemotherapy); differently only 1 of the 10 controls showed mild and focal fibrosis ($p < 0.05$). Fibrotic bands were uniformly distributed in the total mesorectum and were close to the fibrous tissue replacing tumor in the rectal wall. At times, the thickened bands of fibrosis developed a lobulation of the adipose tissue (Figure 1B and 1C) entrapping lymph vascular

Table I. Clinical and pathological features of the 90 preoperative irradiated patients and the 10 not treated controls.

	Irradiated patients (90 patients)	Not irradiated patients (10 patients)
Clinical and pathological features		
Age at diagnosis	67 ± 11,23 years (56–84)	69 ± 14,18 years (61–78)
Male/female	46/44	6/4
Preoperative staging		
uT2N0M0	23	8
uT3N0M0	67	2
Pathological staging		
yT0N0M0	6	-
yT2N0M0	18	-
yT3N0M0	66	-
Regression-grade tumor (Dworak's)		
Dworak 0	25	-
Dworak 1-2-3	59	-
Dworak 4	6	-

structures and nerves (Figure 1D). Within the lobules, an increase of fibroblastic component was clearly evident, with consequent mild reduction of the adipocytes. A concomitant vascular damage was observed in more than half of the treated cases (46/90; 51%), mainly in the groups of the patients treated with 50 Gy irradiation combined with chemotherapy – Group 1 – (39/50 vs 4/20 and 2/20 subjects, respectively, in the three groups $p < 0.05$). The arterial network, represented by branches of small caliber, showed thickening of the tunica media with an abundant mixoid matrix deposition (Figure 2A and 2B), and the intima was hyperplastic with narrowed lumen; at times a micro-thrombosis was observed. Fibrosis surrounding the wall of the arteriole (Figure 2C) and pan-arteritis were clearly detected in more than half cases (Figure 2D and 2E). In the adventitia of the arteriole of 5 patients treated with chemotherapy in association to radiotherapy, an infiltration of eosinophils was evident (Figure 2F). Similar alterations, including a thickening of the wall with narrowing of the lumen and associated micro-thrombus were observed in small veins and in the lymphatic channels, although in smaller quantities than what was observed in the arteries. Occasional findings of complete obliteration of the lumen induced by the fibrosis were observed in the lymphatic channels proximal to tumor-growth margins. Only one of the controls showed unspecific mild signs of inflammation associated to mild edema and mild hyperemia. As reported in Figure 3A and B, the lymph nodes showed necrosis and sclerotic modifications with disruption of the capsule. This finding occurred in 22 of the 90 treated patients (14 subjects in *group 1*, 5 in *group 2* and 3 in *group 3*; 24%) but not in the control cases and with no statistical difference between the three groups. In 12/90 cases (13%), small nerves showed discrete fibrosis, at times associated to lymphoid and plasma cells recruitment (Figure 3C and D). Stated that the histopathological alterations described in our study occurred in the whole mesorectum of the three different treated groups, we failed to define a possible grading score. Even if not statistically significant, in the cohort of 20 cases that underwent surgery within 2 weeks after 25 Gray short-term preoperative radiotherapy, the fibrosis was less intense and mild signs of inflammation were detectable around lymph and vascular vessels and nerves. We did not find any significant correlation between the histological modifications induced by chemoradiotherapy and the Dworak's score of tumor regression and the preoperative c- or post-treatment y- parameters. In the non-neoplastic rectal wall, we observed mucosal damage that varied from erythematous changes to

Table II. Histopathological modifications observed in the 90 irradiated and 10 not treated patients.

	Group 1 50 Gy+FOLFOX (50 subjects)	Group 2 50 Gy (20 subjects)	Group 3 25 Gy (20 subjects)	Controls (10 subjects)	*p*-Value
Fibrous strands in the adipose tissue	50/50	17/20	19/20	1/10	< 0.05
Vascular damage*	39/50	4/20	3/20	1/10	< 0.05
Lymph node damage°	14/50	5/20	3/20	None	n.s.
Perineural deposition of fibrosis	8/50	2/20	2/20	None	n.s

*Includes vasculitis and thickening of the wall of arteries and veins.
°Includes pericapsular fibrosis and complete sclero-jalinosis.
n.s. = not statistically significant.

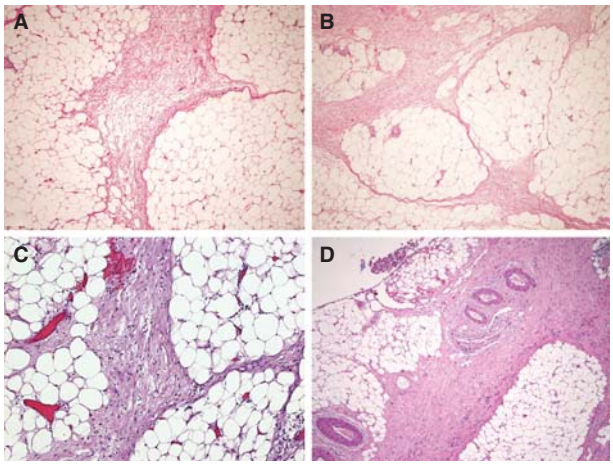

Figure 1. Dense and compact fibrous strands are dislocated in the interstitial component of the irradiated mesorectum (A). At time, thick bands developed a lobulation of the adipose tissue (B and C) and entrapped lymph vascular structures and nerves (D).

micro-ulcerations. In the submucosa, the interstitial lymphoid-associated tissue was scanty or absent, and the wall of the arterioles showed hyalinization and increased thickness. Muscularis mucosae often appeared distorted and replaced by fibrosis.

Discussion

The use of radiation therapy for the cure of cancer involves exposure of the surrounding normal tissue inducing different modifications that vary during the course of the treatment [13–15]. Our study represents a morphological description of the histologic alterations induced in the mesorectum by neoajuvant radiotherapy, alone or associated with chemotherapy. In particular, we focused on the different anatomical components of the mesorectum including adipose tissue, vascular supply and nerves localized external to the tumor site. The most visible histological findings were represented by fibrosis of the adipose tissue, perivascular and perineural fibrosis deposition, vascular damage, revisable in vasculitis or microthrombosis and sclero-hyalinosis of lymph nodes. Although these histopathological findings had been described in the literature as consequences of the

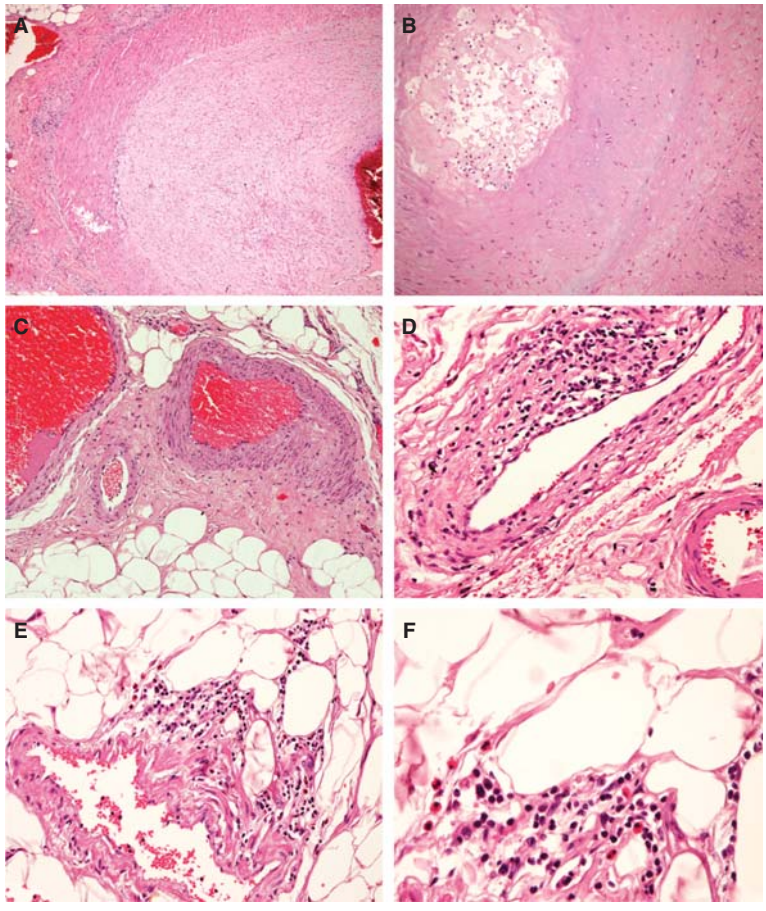

Figure 2. Vascular damage induced by radiotherapy. Thickened tunica media of arteries (A), with presence of myxoid matrix and histiocytes (B) was observed in more than half cases. A perivascular fibrosis surrounding the wall of the arteriole (C) and vasculitis were mainly observed in subjects received neoajuvant chemoradiotherapy (D and E); eosinophils recruitment can be appreciated (F).

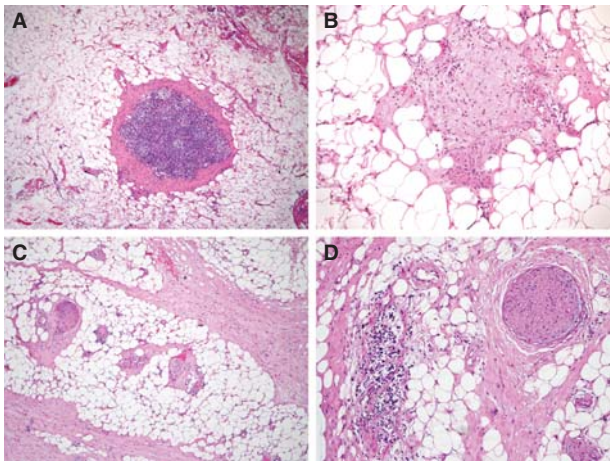

Figure 3. Lymph nodes pericapsular fibrosis and complete sclerohyalinosis (A and B) and perineural deposition of fibrosis (C and D) were observed within the mesorectum adipose tissue, mainly in subjects treated 50 Gy dose radiotherapy associated with chemotherapy.

irradiation of the pelvic region for different malignancies including prostatic, gynecological or rectal cancer [13], no detailed descriptions have been published about them. In our experience, the whole evaluation of the mesorectum tissue, performed through consecutive cut sections, allowed us to establish that these modifications were homogeneously distributed in all mesorectum, up to the resected surgical margin. This data is supported by previous studies that evaluated the development of post-chemoradiotherapy fibrotic spiculations in the mesorectum, using the MR [16]. In literature, diffused hypointense fibrotic tissue projecting the mesorectal fascia is reported in more than 50% of the patients [16]. Although the tangible occurrence of these histological alterations of the mesorectal components demonstrate the actual consequence of the irradiation, it is important to state that their interpretation should be done with caution. In particular, it could be important to consider the time span between the radiotherapy and the mesorectal resection and the possible correlation with it [16,17]. In this period, a continuous remodeling process occurs in the tissue with subsequent changes in the cellular and extracellular microenvironments. These changes could lead the pathologist to overestimate them. In our study, we focused the attention on the part of the mesorectum distant from the tumor site being, this last, more susceptible to restore, in order to exclude the histological modification induced by the necrotic tumoral tissue replaced by fibrosis (post-treatment scar). It is well known that in the irradiated tissue, the histopathological changes are dose-related, occur immediately after the radiation exposure and are visible in weeks, months or even years after treatment [13,17–22]. In our cases, the mesorectum treated with high doses of radiotherapy (50 Gy) showed diffuse and intense fibrosis and vascular damage, becoming more evident, whereas radiotherapy was associated with chemotherapy. Thus, the alterations could be the result of the combination of both treatments [18].

The pathways underlying the abnormalities occurring in the irradiated mesorectum reflect the effect of the radiolysis on the immunological system, explicating in particular in the activation of the leukocytes, most probably, through the release of the cytokines [13,18,22–24]. The accumulation of inflammatory cells, particularly evident in the perivascular recruitment of lymphocytes and eosinophils, and in the activation of fibroblasts in the connective tissue, has been demonstrated in patients treated with radiotherapy [22–24]. In our study, mainly in the cases who received radiotherapy plus chemotherapy, we observed accumulation of inflammatory cells around the vessel and the nerves composed by lymphocytes, plasma cells and eosinophils. As a consequence of the inflammation, the deposition of collagen and the increase of extracellular matrix substance and a remodeling processes that lead to fibrotic strands in the adipose tissue and the myxoid thickening of the arterial walls [18,22–24]. Some authors, using animal models, evaluated the chronic macro- and micro-effects of the irradiation in the tissue and described particularly a vascular damage with degeneration of the vessel wall, dilated capillaries and reduction in their density [17,24]. Moreover, some studies have demonstrated that normal lymphatic tissue as well as metastatic lymph nodes are reduced by irradiation [25,26] and that doses higher than 25 Gy are required to cause damage to the peripheral nerves [16,17]. In our study, we considered only previously defined N0-tumors by CT or MRI, and histologically confirmed to be macro- or micro-metastatic-free tumors. Furthermore, we observed an overall reduction of the lymphoid component in the mesorectum confirming the involution process of lymph nodes induced by the therapy [13,16,25,26]. As reported in literature, high-dose radiotherapy induces lymphocyte depletion, atrophy of the stroma and adipocytes replacement, leading to unrecognizable lymph nodes during histological examination of the mesorectum samples [26].

Based on our histological evidences, it can be argued that the other pelvic structures, like the residual rectal stump, the anal canal, as well as the sphincter muscular apparatus, could also be affected by the same modifications described in the mesorectum. This could explain the well-known incidence of the postsurgical clinical complications that are observed at short- and long-term sequels. In particular, the

vascular damage can lead to anastomotic fistulas, the fibrosis can induce strictures, while the perineural fibrosis could give reason for the sphincter functional disorders [13,27–29]. Concerning the importance of the complete mesorectal excision, the pathological modifications observed ubiquitously in the mesorectum could reinforce the importance of this surgical approach.

Concluding, our observations represent the morphological description of the histopathological alterations induced by adjuvant radiotherapy in the different mesorectal anatomical components. Although with limitations, they could give some possible explanations among their possible clinical relevance including post-operative complications and sequels.

Acknowledgments

A special thanks goes to ARTI (Associazione Ricerca Tumori Intestinali) for the scientific support, MS. Angela Iuliano for the collection of the pathological data, and the technical support from the staff of the Pathological Anatomy of Modena with particular mentions to MSS Federico Federica, Zaramella Rosa and Silvia Malaguti.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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