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Review

A Ten-year-long Update on Radiation Proctitis Among Prostate Cancer Patients Treated With Curative External Beam Radiotherapy

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Abstract. *This comprehensive synopsis summarizes the most relevant information obtained from a systematic analysis of studies of the last decade on radiation proctitis, one of the most feared radioinduced side effects among prostate cancer patients treated with curative external beam radiotherapy. The present review provides a useful support to radiation oncologists for limiting the onset or improving the treatment of radiation proctitis. This work shows that the past decade was a harbinger of significant new evidence in technological advances and technical tricks to avoid radiation proctitis, in addition to dosimetric perspectives and goals, understanding of pathogenesis, diagnostic work-up and treatment. We believe that a well-rounded knowledge of such an issue is fundamental for its appropriate management.*

The standard treatments for organ-confined prostate carcinoma are radical prostatectomy or curative radiation therapy with or without anti-androgen drugs. There is no clear advantage in terms of cancer-related overall survival between these two therapeutic approaches; the choice of treatment is discussed among surgeons and radiation oncologists with the patient who chooses how to proceed. Irradiation is an organ-preservation therapy that has some advantages with respect to the surgical approach. In fact, patients submitted to radiotherapy have no anesthesiological risks and a lower incidence of both erectile dysfunction and urinary incontinence. Besides, there is no "strict" age-linked or comorbidity-related contraindication to irradiation.

In the last years, a tremendous amelioration in radiation delivery techniques and planning technologies has made radiation treatments even safer with a lower incidence of radiation-related adverse events. However, to date, there are some concerns with respect to gastrointestinal and genito-urinary toxicities, which, in some instances, could determine an interruption of radiotherapy and a lower quality-of-life for patients. Finally, in the most severe cases of anorectal toxicity, aggressive surgical treatment may be necessary to control bleeding or mucosal necrosis.

The aim of this paper is to provide novel key insights into recent technological and pharmacological advances, as well as on possible conceptual reforms, which, within the perspective of a translational medicine, could assist the radiation oncologist in a more careful management of radiation proctitis (RP) among prostate cancer patients treated with curative external beam radiotherapy (EBRT). In particular, we focus our interest on the relevant literature published over the past decade.

Materials and Methods

We queried the PubMed database with 4 search terms: "radiation", "proctitis", "prostate" and "cancer". We limited the scrutiny of bibliographic entries to articles published from 01/01/2010 to 31/12/2020. The most used technique to deliver irradiation is external beam radiation therapy (EBRT) and therefore, we have excluded the works concerning the treatment of prostate cancer with stereotactic radiotherapy (SRT), proton beam (PBT) or carbon ion radiotherapy (CIRT) and with brachytherapy (BT) (or exclusively with its associations, *e.g.* EBRT + BT), types of radiotherapy (RT)

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of particular complexity and which can lead to a different procedure- or dose-related toxicity profile. Only papers about definitive and adjuvant RT have been selected, excluding those inherent with investigational preoperative settings, as well as reirradiation, curative RT for rare patient subsets (*i.e.* prostate cancer patients with inflammatory bowel disease). We also disregarded studies on other cancers and/or other radiation induced side effects (*i.e.* urinary symptoms) or related to special procedures (*i.e.* rectal spacer injection etc.) and those primarily concerned with cost-effectiveness analysis or territorial surveys. Moreover, we excluded duplicates, case reports and case series with less than 5 patients, articles not available in English or concerning alternative medicine, editorials and commentaries. We also examined all the studies referred to in the retrieved articles, so as not to miss functional articles for the aim of this work. The collection and analysis of bibliographic resources were conducted according to the PRISMA method (Figure 1) and to the following PIO process: Population (prostate cancer patients), Intervention (EBRT, not BT, SRT, PBT or CIRT), Outcome (RP) (Table I).

Results and Discussion

The search conducted on the basis of the abovementioned time criteria produced 178 results, among which 76 papers were selected according to their relevance for the purposes of this work. Such studies are discussed in detail in the following paragraph, which is further divided into subparagraphs based on the particular topic of the retrieved articles. A few limited bibliographic entries prior to the above time limit have also been included, as they are considered functional to our analysis.

Literature overview. As exemplified by the assessment scales of the leading European and American scientific societies, the most common symptoms experienced by patients with RP are tenesmus, mucorrhea, pain and bleeding that, from the acute phase, can end in the chronic phase, when fecal incontinence, necrosis and fistula formation could arise (1-5). Nakamura *et al.* (6) clearly summarized what factors are associated with proctitis, stating the total radiation dose, fractionation regimens, dose parameters of the critical organs, beam delivery techniques and treatment plan quality as crucial for perception of post-radiation quality of life among prostate cancer patients. Since the clinical review by Garg *et al.* (7), which indicates the incidence, clinical manifestations, radiation-related and patient risk factors, workup and treatment of proctopathy, new scientific evidence has emerged, more functional and suited to the needs of current clinical practice in radiotherapy.

Technological advances. On the technological side the recent real-world population-based work conducted by Sujenthiran *et al.* confirms the significant advantage in terms of reduction of gastrointestinal (GI) toxicity among prostate cancer patients treated with intensity-modulated radiotherapy (IMRT), compared to the 3D-conformal radiotherapy (3D-CRT) (8). As a result, IMRT delivered by modern medical linear accelerators (LINACs) removes all sorts of concerns expressed by Roach (9) concerning quality assurance procedures. Bekelman *et al.* (10) had anticipated Sujenthiran's conclusions, reporting a hazard ratio (HR) for proctitis of 0.78 in favor of intensity-modulated irradiation technique with respect to 3D-CRT in elderly men with nonmetastatic prostate cancer. These results can be further improved by an IMRT guided by a daily online imaging for a more accurate set-up verification and a more precise dose delivery, as demonstrated in a randomized controlled trial conducted by Wortel *et al.* (11, 12). These authors compared image guided IMRT (IG-IMRT) and 3D-CRT for prostate cancer treatment and reported a significant reduction in acute and chronic proctitis rates in favor of the former ([odds ratio (OR)]=0.54 and HR=0.37, respectively, $p \leq 0.005$), as well as acute genitourinary (GU) toxicity (OR=0.59), but did not confirm this for chronic GU toxicity (HR=1.19). The value of a correct set-up verification through dedicated imaging would even seem to outweigh the characteristic dose conformity of IMRT. In fact, Hama *et al.* (13) found excellent disease control outcomes and toxiciy rates with a rough adaptive radiotherapy technique without the use of a multileaf collimator: their method consisted of a first phase during which the prostatic planning target volume (PTV) was irradiated with 2 Anteroposterior/Posteroanterior fields up to a dose of 46 Gy in 2 Gy/fractions, followed by a second phase up to a dose of 76 Gy with 2 opposed lateral fields with edges adapted in real-time on daily cone beam computed tomographies (CBCT) and shaped through lead block positioning on the anterior wall of the rectum in order to maximize its sparing. These authors reported a 5-year incidence of grade 2 gastrointestinal adverse events of only 3.8%, compared with a lasting local relapse-free survival rate of almost 100%. Even though the same RT techniques were used [3D-CRT and volumetric modulated arc therapy (VMAT)] for immediate post-operative or salvage purposes, Vogel *et al.* (14) and Borghetti *et al.* (15) reported directly opposite results in terms of rectal toxicity: the former reported a higher risk of proctitis for immediate postoperative RT while the second did not show a better tolerance for salvage RT, but only for VMAT, with respect to 3D-CRT (6.3% *vs.* 28.4%, $p=0.006$), as seen in the immediate postoperative RT group of Vogel's clinical study ($p=0.02$). The reason for such apparently divergent results may lie in the fact that patients treated with VMAT by Borghetti *et al.* could rely on image guided set-up verification, unlike those treated by Vogel and colleagues. The reliability of modern IG-IMRT techniques allows for a safe delivery of hypofractionated doses that in a work by Vassis *et al.* (16) proved to be even less toxic than conventional fractionation. In this case, it should be

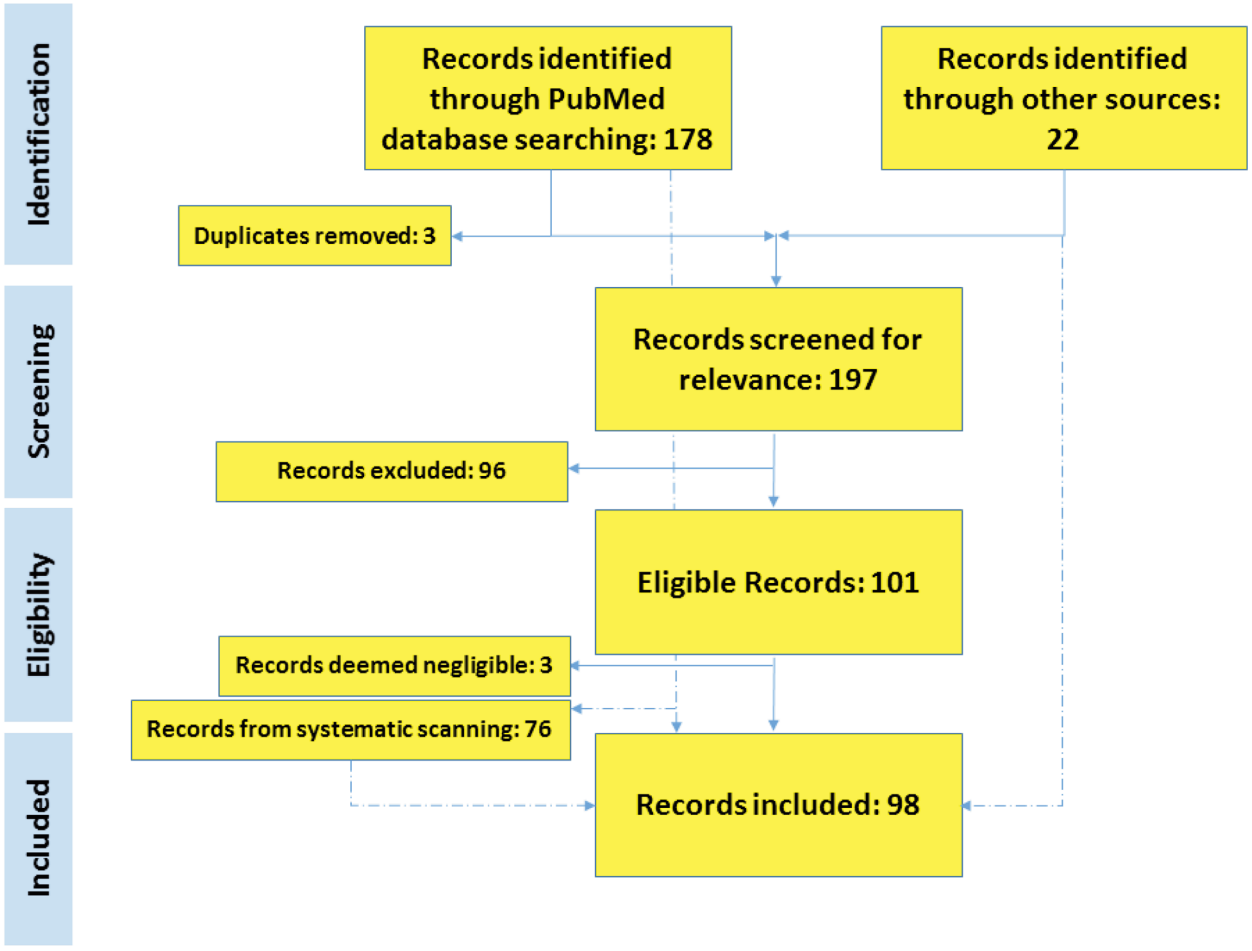

Figure 1. *Preferred reporting items for systematic reviews and meta-Analyses (PRISMA) flowchart.*

emphasized that hypofractionation also constitutes a financial health benefit, since shortening the total treatment time allows for a reduction in health care costs and the extension of oncologic treatments to a wider population. However, these results do not agree with those previously analysed and discussed in the clinical review and large meta-analysis by Datta *et al*. (17), as these authors assign a greater risk of acute GI toxicities to hypofractionation than conventional fractionation (risk ratio=1.470). Although the size of the investigated population in the meta-analysis by Datta *et al*. (n=8,146) far exceeds that of the sample enrolled in the work of Vassis (n=110), it is extremely heterogeneous, as it includes patients irradiated with 2D-, 3D-CR-, IM- and IG-IM-RT, while not providing sufficient details on the risk of proctitis for patients treated with IG-IMRT, which is probably the discriminator to which the low rectal toxicity rate can be attributed in the case of Vassis *et al*. In the work conducted by Mohammed *et al*. (18), external beam - image guided radiotherapy (EB-IGRT) was found to be worse, in terms of acute and chronic GI toxicity, than the other two compared techniques [brachytherapy (BT) alone and EBRT + BT]. In this case, the increased frequency of tenesmus and diarrhea during the acute and chronic rectal bleeding phases could be heavily influenced by two factors: 1) the average larger prostate size of patients treated with exclusive EB-IGRT could have resulted in a higher dose to the rectum and

Table I. *Extraction fields using population, intervention and outcome criteria.*

Category	Extraction fields
Population	Prostate cancer patients
Intervention	EBRT, not BT, SRT, PBT or CIRT
Outcome	Radiation Proctitis

2) 60% of the above patients had been treated with 3D-CRT. This latter technique has a lower dose conformity than the IMRT counterpart (40%); such a difference could turn in a higher damage of the rectum. Gill *et al*. (19) examined the different patterns of radio-induced toxicity between prostate cancer patients irradiated with and without IGRT, reporting a lower rate of proctitis and haemorrhoid symptoms of borderline significance (p=0.06) in favor of IGRT. Statistical significance was subsequently achieved for prostate cancer patients verified with cone beam Kv CT (CBKvCT) *versus* those verified with electronic portal devices (EPIDs) in the work of Conde-Moreno *et al*. (20). The irreplaceability of a live IGRT lies in the demonstrated inadequacy of an off-line adaptive process used to define a PTV depending on variation in prostate position: indeed, Parzen *et al*. found a significantly higher rate of rectal toxicity among patients treated with an Image-Guided Adaptive Radiation Therapy, compared to those treated with BT (21). The ultimate achievement of the IGRT potential derives from works such as those of D'Agostino *et al*. (22), who published acceptable rectal toxicity rates (<20%) in patients with prostate cancer treated with ultrahyprofractionated VMAT and Real-time Electromagnetic Tracking.

Technical ploys. The rectum, albeit a fixed organ in the pelvic cavity, is subject to significant volume changes depending on its gas and stool content that can compromise its exclusion from the radiation field. Various technical solutions have been proposed in order to mechanically limit radiation exposure to the anterior rectal wall, including the application of a hydrogel spacer via transperineal injection in the interspace between the prostate and rectum. This is characterized by an extremely low procedural hazard (<2%) (23) and is particularly beneficial in allowing a reduction of rectal volume inside the 70 Gy isodose from 6% to 2% (24). This medical intervention has been shown to be effective in significantly reducing chronic RP (25). Mahdavi *et al*. (26) achieved the same result using a rectal retractor (RR), whose application reduced the dose and dose – volume parameters to the rectal wall, especially for its anterior portion. Such a ploy implied an average reduction of 44.0% in Grade 2 rectal bleeding in the normal tissue complication probability (NTCP) analysis, when compared with and without RR plans. Among other things, the *in vivo* measured dosimetry that is performed simultaneously to the treatment delivery, proved to be sufficiently coherent with the planned dose (67%), although not reaching the very low discrepancy (82%) highlighted by Wootton *et al*. (27), who used another immobilization device, the endorectal balloon. The aforementioned medical device, in addition to ensuring the prostate immobilization for a more accurate radiotherapy, allows a remarkable anterior rectal wall sparing by its dosimetric effect derived from the presence of an air-tissue interface, without compromising the dose coverage for the prostate, as shown by Teh *et al*. (28). Rastogi *et al*. (29) demonstrated that online translational corrections guided by daily kV-CBCT carried a significantly lower risk of grade ≥2 proctitis if, after merging with CT simulation images, anatomical matching was conducted by fiducial gold markers rather than by bony landmarks (38 % *vs*. 5.8%, OR=10.1), emphasizing the usefulness of prostate fiducial marker placement, especially for current clinical practice of dose escalation. All these findings support a dose delivery to the prostate ≥74 Gy for a theoretical better local control. However, the usefulness of such a prescription is questioned by the works of Meng and Lee *et al*. (30, 31) that did not show a therapeutic gain with escalated doses, intended as prolongation of overall and biochemical recurrence free survival, but only a higher rate of moderate-severe rectal toxicity. Clinical Target Volume (CTV) delineation on Magnetic Resonance (MR) images did not reduce the risk of proctitis, but only urinary disorders according to Sander *et al*. (32). Lafond *et al*. (33) have shown that optimization of the treatment plan by means of segmentation of the rectum into subvolumes to which stricter dose-volume constraints are applied, decreases the mean dose up to 7.7 Gy in the risk area. This corresponds to a reduction rate of rectal bleeding equal to 22%, while preserving an adequate target dose coverage.

Dosimetric issues. The fact that the escalated dose corresponds to a greater risk of grade ≥2 proctitis is confirmed by the MRC RT01 Trial with HR equal to 1.64, when comparing localized prostate cancer patients treated with 3D-CRT for a dose of 74 Gy with the ones limited to 64 Gy (34). Jensen *et al*. (35) showed that narrower margins of target volumes carried a lower risk of grade ≥2 proctitis for IMRT than for 3D-CRT plans, according to NTCP predictions. The dose-volume constraints for rectum mostly referred to are those published by Michalski *et al*. (36): V50 <50%, V60 <35%, V65 <25%, V70 <20%, and V75 <15%. Compliance with the above limits corresponds to a risk of Grade ≥2 and Grade ≥3 late rectal toxicity less than 15% and 10% respectively, at doses up to 79.2 Gy, in 1.8-2 Gy/day fractions. Furthermore, these authors remark that a percentage reduction, albeit of the same order of magnitude (*i.e*. 5% in V75 *vs*. V50), has a clearly different positive prognostic value if achieved at the higher doses and hypothesized that the substantial reduction in the volumes exposed to intermediate doses obtainable with IMRT vs 3D-CRT may be important in determining a lower toxicity. The robustness of the constraints proposed by Michalski is confirmed by the results reported by Fuentes-Raspall *et al*. (37). Pederson *et al*. (38) showed that keeping even stricter dose-volume constraints, such as rectal V70 ≤10%, V65 ≤20%, and V40 ≤40%, practically eliminates the risk of grade ≥2 late proctitis, measured after 4 years. Subsequently there was a gradual conceptual evolution, as in the work of Buettner *et al*. (39) who proposed that the dosimetric approach, more

effectively predictive of risk of rectal toxicity, was the one that went beyond the volumetric concept moving towards the shape and location of the dose distribution, thus suggesting the predilection for Dose Surface Histograms (DSH, computing the dose in voxels corresponding to the surface of rectum) over Dose Volume Histograms (DVH). These authors indeed demonstrated a significant correlation with the lateral extent of doses ≥61 Gy exceeding 55% of the circumference of the rectum. In addition, DSH correlated with proctitis for doses ≥59 Gy. Hamlett *et al*. (40) used a similar approach to the matter: they showed a significant correlation for grade 2 late proctitis with DVH and DSH ranges between 25-36 Gy, even stronger than that found for doses of 61-67 Gy. The results about hypofractionated doses published by Arunsingh *et al*. (41) conceptually agree with Buettner's, having shown that the absolute rectal volume is more effective than relative volume in predicting the risk of rectal toxicity. The recommended absolute dose-volume parameters for predicting grade 2 acute proctitis were VEQD2-60Gy <9.7cc and VEQD2-50Gy <15.9cc. Also, Ozkan *et al*. (42) showed a significant correlation of RP only with total rectal volume but not with relative dose-volume parameters (V50, V60, V65, V70 and V75) or even the rectal volume included in PTV. Similarly, Kotabe *et al*. (43) suggested that dose-volume constraints referring only to the absolute rectal volume are more reliable. They demonstrated how a rectal D5cc ≥60 Gy is significantly associated with late ≥ grade 1 rectal bleeding in IG-IMRT, while the relative rectal volume was not. The results published by Mirjolet *et al*. (44) were along the same lines: the absolute volume of the rectum between 25 Gy and 50 Gy correlates significantly with acute toxicity rate, while their relative counterpart does not. These findings were contradicted by the results published by Paleny *et al*. (45) that reaffirm the correctness of the dosimetric evaluation for the prediction of proctitis referring to the relative and not to the absolute rectal volumes, except for V50Gyccm, which is the only absolute dose volume parameter statistically associated with acute proctitis. Thor *et al*. (46) suggest that both absolute and relative dose-volume relationships could affect the risk of proctitis. Indeed, it is important to define the absolute rectal volume that receives equal or more than 35 Gy and the minimum dose delivered to the 5% of the rectal volume, emphasizing the need for a reduction of hot spots (≥65 Gy). Also, Ng *et al*. (47) dwell on high doses having reported that a V70 >14% was significantly more frequent among patients affected by late proctitis. A higher prescribed radiation dose among prostate cancer patients surveyed using the Expanded Prostate Cancer Index Composite questionnaire was significantly related to a progressive 10 year-long worsening of stool incontinence and rectal bleeding (48). Martínez-Arribas *et al*. (49) reported a greater risk of proctitis with a mean rectal dose >45 Gy. Sanguineti *et al*. (50) proposed the following relative dose-volume constraints in order to minimize the risk of late rectal bleeding when delineating the rectal wall (thickness of 3 mm) and treating prostate target with moderately hypofractionated radiotherapy (62 Gy in 3.1 Gy/day fractions): V32 ≤50%, V50 ≤25.8% and V60 ≤10%. The systematic review by Olsson *et al*. (51) included, among other things, two studies that proposed rectal volume thresholds for doses ranging from 23 (<80%) to 69 Gy (<15%) in order to limit the risk of proctitis using the DVH method. The dosimetric investigation that aims to verify the correspondence between the planned dose and the delivered dose to the rectum has been developed recently. Shelley *et al*. (52) were the first to reproduce the Dose Surface Maps (DSM) on daily MegaVoltageCT image guidance scans and to generate an accumulated DSM, representitive of the actual total delivered dose. They reported that accumulated DSMs had stronger correlations with rectal bleeding and proctitis, than planned DSMs, with particular reference to quantitative and qualitative spatial distribution of doses ≥50 Gy. Subsequently Casares-Magaz *et al*. (53) used a similar approach to confirm the discrepancy between the delivered and the planned dose, especially in the inferior sector of the rectum: the extent of high accumulated dose (≈70 Gy) at this level correlated with late GI toxicities. Interestingly, DVH/DSH-based metrics have been proven to be inadequate in finding relationships with symptomatic outcomes. It could be hypothesized that daily on-board CT-imaging can serve as a basis not only for calculating the accumulated DSM, but also for radiomics analysis with the aim of early extracting predictive features of the development of proctitis, as Mostafaei *et al*. (54) managed to do from pre-treatment CT scans.

Increased understanding of pathogenesis and predictive signatures supporting possible therapeutic implications. Since the works by Gambacorta, Heemsbergen, Barnett *et al*. (55-57) who highlighted that late rectal damage was consequential to the persistence of an unhealed acute injury, mainly due to inflammatory mediators, new data have emerged which, in addition to increasing knowledge of the pathogenesis of such a radioinduced adverse event, could lay the groundwork for the development of new drugs capable of limiting its occurrence. Beaton *et al*. (58), for example, compared blood samples from 10 patients that developed grade 3 proctitis with analogous ones collected by 20 patients that experienced no rectal toxicity: they irradiated the blood samples at 6 Gy and observed greater lymphocyte radiosensitivity among patients with grade 3 proctitis. They were then able to offer a valuable predictive indicator for developing a tailored radiotherapy. Ghorbanzadeh-Moghaddam *et al*. (59) demonstrated that Vitamin D deficiency predisposes to the development of severe acute radio-induced proctitis, promoting its correction when necessary. The increased expression of vascular endothelial growth factor (VEGF) in response to radiation damage could

be the basis of clinical symptoms and endoscopic rectal mucosa changes in patients with chronic proctitis: it seems responsible for abnormal sprouting angiogenesis, which endoscopically manifests itself with telangiectases tending to easily bleed (60). Microvascular density was significantly increased in post-irradiated rectal mucosa biopsies and related to an increased expression of VEGF and CD31, similarly to the work of Karamanolis (61). A dysfunction at the baseline of the mucosal microvasculature could be at the root of the greater susceptibility of developing proctitis, as hypothesized in the work of Alashkham *et al*. (62). The enhanced radiation-induced normal tissue damage, such as proctitis found in diabetics due to a pro-oxidative microenvironment, could be counteracted by MnTE-2-PyP, a manganese porphyrin capable of cytoprotection for fibroblast cells of diabetic prostate cancer patients submitted to radiotherapy, without obstructing radiation mediated cancer cell death, as claimed by Chatterjee *et al*. (63). Kosmacek *et al*. (64) suggested that damage to fat reservoirs could favor radio-induced rectal fibrosis. Actually, it could trigger myofibroblast formation at the level of the pelvic organs that are unintentionally irradiated. Indeed, adiponectin protects fibroblasts from radioinduced cell death, but not prostate cancer cells in mouse models. Campostrini *et al*. (65) found that a substantial biopsy-proven gland and crypts loss in anterior rectal wall following irradiation could be considered strongly predictive of late proctitis. These authors recommended delivering a mean dose ≤48-52 Gy to the anterior rectal wall to minimize the depletion of both rectal mucosal gland and crypts. As expected, Luo *et al*. (66) reported that a larger Gross Tumor Volume (GTV) in patients with locally advanced prostate cancer carries a significantly higher risk of grade G2-G3 acute proctitis, likely due to a greater area of the anterior rectal wall exposed to the high radiation dose. They recorded a HR of 2,132 by comparing GTV greater or equal than and lower than 141 cc and relied on the effectiveness of neoadjuvant androgen deprivation therapy to reduce the prostate size (67). Pathak *et al*. (68) assume an individual genetic predisposition to the development of proctitis in patients irradiated for adenocarcinoma of the prostate, involving mainly polymorphisms of genes responsible for DNA repair and mithocondrial function. In a large meta-analysis by Kerns *et al*. (69) one single nucleotide polymorphism (SNP), rs17055178, is indicated as significantly associated with the risk of proctitis among the retrospectively collected European ancestry cohorts; however, it was not confirmed in the prospectively accrued Japanese cohorts. Similarly, the REQUITE project is a trial to validate predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality of life in cancer survivors (70). In the latter cohort of patients, Massi *et al*. (71) isolated, by means of a deep learning approach, eight SNP signatures that could identify patients most likely to experience adverse effects after radiotherapy for prostate cancer. The genetic susceptibility to develop RP could also have a cancer-specific prognostic value. Eade *et al*. reported that acute epithelial toxicity after RT for prostate cancer could be considered predictive of tumor radiosensitivity and control. By comparing patients with and without acute toxicities, they observed a gain in terms of freedom from biochemical failure at 5 and 10 years in favor of the former group (72).

Diagnostic work-up. After a careful physical examination and clinical history, proctoscopy plays a key diagnostic role, as well as a prognostic one, as recently highlighted by some studies. In fact, in the work of Campostrini *et al*. (73), proctoscopy was proven to have a good positive predictive value (86.67%) but low sensitivity (19.4%). In particular, a significant agreement between acute endoscopic proctitis (AEP) and acute clinical proctitis (ACP) was observed in 13/15 cases. To be thorough, we remark that, within a sample of 67 acutely symptomatic patients, only 13 had a positive endoscopic finding. Furthermore, the combination of ACP and AEP implies a fivefold risk of late clinical proctitis (p=0.001), which is much greater than that found in patients with ACP only (HR=2.1, not significant). The prognostic value of proctoscopy can thus support the physician in putting an option for an early and more effective therapy. Furthermore, proctoscopy is able to detect a regression of mucosal damage even up to 65 months after radiotherapy, quantifiable in an improvement rate of 67% in the work of Goldner *et al*. (74). These authors found, at first evaluation, telangiectasias in 75% of the patients, mainly on the more radio-injuried anterior rectal wall area (distal section), and congested mucosa affecting the whole circumference in 50% of patients. However, they did not indicate how many of these endoscopic findings were actually symptomatic.

Treatment. The readers of this paper can refer to the review recently published by Grodsky *et al*. (75), which offers an exhaustive overview on possible therapeutic strategies for different grades of radiation proctopathy. They mention, as effective options, among others: sucralfate, anti-inflammatory medications and/or steroids as first line therapy for patients with mild symptoms, formalin instillation or endoscopic argon plasma coagulation (APC) in cases of significant or refractory bleeding as well as surgical procedures, in severe refractory cases, even though they are burdened by high morbidity and mortality. The results published by Takemoto *et al*. (76) are derived from daily evidence-based practice and agree with the aforementioned therapeutic recommendations: observation, steroid suppositories/enemas or APC, mostly as salvage therapy. These authors suggest limiting the prolonged use of corticosteroids, having recorded a death from septic shock in their cohort; however, that finding was likely

unrelated to drugs administration. A low-dose acetylsalicylic acid therapy is yet to be demonstrated as clinically effective in decreasing the severity of radiation-induced mucosal inflammation in the rectum, as already shown in wistar rats by Doi *et al*. (77). Amifostine can be effective in reducing radioinduced damage among prostate cancer patients treated with radical hypofractionated accelerated radiotherapy, as shown in a clinical trial by Koukourakis *et al*. (78). Stefanelli *et al*. (79) tested the effectiveness of hyaluronic acid suppositories compared to placebo; they reported only a significant delay on the onset of proctitis in favor of hyaluronic acid (p=0.04), but not a statistically significant difference in its rate between the two groups (p=0.08). Sucralfate paste enemas have been proven to be successful in leading to a discreet improvement of haemorrhagic RP in a series of 23 patients (80). However, oral administration of sucralfate does not provide an additional clinical benefit when paired with APC sessions for chronic haemorrhagic RP (81). In a clinical trial conducted by Maggio *et al*. (82), daily sodium butyrate enema showed no efficacy in reducing the incidence, severity and duration of acute RP. This adverse event was significantly related only to preexisting clinical status (*e.g*. diabetes or hemorrhoids). Alashkham *et al*. (83) showed that hypertensive prostate cancer patients, taking angiotensin-converting enzyme (ACE) inhibitors during radical radiation therapy combined with hormone therapy, developed significantly lower high grade proctitis compared to non-hypertensive patients or hypertensive patients not taking ACE inhibitors. Jensen *et al*. (84) managed to convey a semi-synthetic glycosaminoglycan (GAG) to the rectal mucosa through a gel composed of silk-elastinlike protein polymers, specifically designed to enhance topical absorption of GAG. They documented a good effectiveness of this medical device in mouse models. Similarly, a pilot randomized trial about the effectiveness of intra-rectal administration of epinephrine, whose rationale lies in its radio-protective ischemizing effect, has not achieved the expected goal in reducing the rate of RP (85). Sahebnasagh *et al*. (86) demonstrated that Aloe vera topical ointment could be effective in prevention of RP; this finding is particularly notable given the non-existent toxicity profile of this product. In a randomized controlled phase II trial conducted by Saadipoor *et al*. (87), oral nanocurcumin was not superior to placebo in preventing or mitigating symptoms of proctitis in patients undergoing RT for prostate cancer, but this fact could be due to the lack of a sufficiently large sample size to identify a statistically significant difference (underpowered study). Nascimento *et al*. (88) showed, in another randomized controlled trial, the protective ability of symbiotics such as Lactobacillus reuteri, at the level of rectal mucosa. APC seems highly effective in stopping chronic rectal bleeding refractory to medical treatment; in the experience of Swan *et al*. (89); a single-session was sufficient in 68% of cases (34/50), while a second session achieved a success rate of 96%. This medical procedure worked well even in all 16 patients in whom previous treatment for chronic RP failed, but 17/50 patients complained about short-term complications (<6 weeks), such as proctalgia (13), rectal mucous discharge (4), incontinence (1), fever (1), and bleeding (1), and only one a long-term complication, *i.e*. an asymptomatic rectal stricture. Likewise, in the work of Hortelano *et al*. (90) APC controlled or reduced bleeding in almost all patients (28/30), triggering only a grade 2 rectal ulceration and a grade 2 rectal incontinence, which spontaneously fully recovered after six months and persistently regressed to grade 1 toxicity at 34 months, respectively. These findings should be regarded with cautiousness as Weiner *et al*. (91) reported post-APC ulceration in 8 cases (22.9%) plus 2 life-threatening toxicities (5.7%), including rectovesicular fistula, one of which actually resulted in the patient's death, probably due to a very short session interval (<24 h). APC was also compared to formalin in a randomized controlled trial carried out by Yeoh *et al*. (92), who showed an excellent effectiveness for both medications in long-lasting control of chronic radio-induced rectal bleeding, but also unresolved anorectal symptoms, or even an asymptomatic worsening of rectal compliance and anorectal sensory function, in most patients. Topical instillation of a solution of 4% formalin was well-tolerated and effective in stopping rectal bleeding in a mixed cohort of patients (prostate and vaginocervical cancer), having the advantage of repeatability due to its safety profile (93). These results have been confirmed by Viani *et al*. (94) that showed a global efficacy rate equal to 94% in 35 prostate cancer patients previously submitted to radiotherapy without any serious side effect and need for blood transfusion. In a study by Clavo *et al*. (95) with a small sample size (12 prostate cancer and 5 gynecologic cancer patients), ozone therapy was shown to be useful in the management of persistent radioinduced rectal bleeding, but this finding needs further confirmation by larger clinical trials. In addition, hyperbaric oxygen (HBO) is one of the most-documented alternative therapies. In a prospective cohort study by Oscarsson *et al*. (96) it has been proven to be effective in 89% of patients with late RP, leading to a significant long-lasting relief of symptoms. Specifically, just after the treatment they recorded a relative improvement equal to 24%, almost confirmed (21%) at 6 to 12-month follow-up. Neither seizures nor otic barotrauma due to oxygen toxicity were experienced by any patient. In an observational study by Andren *et al*. (97) the symptomatologic improvement was in the amount of a reduction of 3.8 in the LENT-SOMA score for late RP comparing pre- and post-treatment conditions (p=0.004) with no significant adverse events. Radiofrequency ablation is an alternative therapeutic option, shown to be an effective treatment by Rustagi *et al*. (98); permanent stoppage of rectal bleeding was achieved in all patients. If chronic proctitis

establishes itself in a context of a hemorrhoidal disease, rubber band ligation of such a venous plexus might be necessary and should be associated with one of the above therapies (99). Also diverting colostomy is an effective solution capable of restoring satisfactory hemoglobin levels and significantly improving the quality of life of patients suffering from severe hemorrhagic chronic RP (100). Recently a novel approach using colonic water irrigation and oral antibiotics demonstrated the efficacy of this kind of treatment in a randomized controlled trial (101). Another endoscopic-guided treatment is the application of Purastat, a haemostatic agent, which was demonstrated to be successful in 21 patients with severe RP (102). Lastly, the recent review by Weiner *et al*. (103) efficaciously summarizes all endoscopic and non-endoscopic approaches for the management of radiation-induced rectal bleeding currently used in daily clinical practice.

Conclusion

Accurate patient positioning and set-up verification are the best tools to prevent RP (104). Traditional DVH constraint analysis systems seem reliable; however, new approaches to assess the rectal dose are gradually carving out more space in clinical practice, as they are potentially more effective in predicting the risk of proctitis, such as by means of DSM. From this perspective, the rectum emerges as a serial organ at risk (OAR), which it actually is, and for this reason the dose absorbed by its subvolumes, quantified in cubic centimeters and not in percentage, is of particular importance in determining the risk of developing RP. The spacing of the rectum from the radiation field through hoc spacers, as well as other technical tricks, is equally effective in lowering such a risk. In recent years, new evidence has been provided about the pathogenesis and treatment of RP. This is a topic of enormous interest among radiation oncologists and a more mature knowledge of it will allow for a better management of this issue.

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