

Argon gas in the management of radiation proctitis - Effective and safe for everyone?

Radiation therapy (RT) is a medical specialty with over one century experience that is commonly used as part of a strategy for the multidisciplinary management of tumors involving pelvic organs. The first cure report with RT dates back to 1899, and the technique has consistently evolved ever since. Until 1980 planning was undertaken using plain x-rays and 2D verifications. CT, MRI, US, and PET have been subsequently incorporated, followed by complex 4D radiotherapy systems that consider physiologic organ movement already in the 21st century. All these advances aim at acquiring virtual images of the volumes to be treated allowing the delivery of higher doses for more effective tumor eradication while minimizing radiation to healthy tissues. The implementation of all these novel technologies has led to a decrease in the incidence of complications (1). Despite efforts to focus radiation on the involved area, actinic proctitis remains a significant side effect of pelvic RT, its acute form being reported –at least transiently– in virtually all patients whereas chronic involvement has an incidence ranging from 5 % to 20 % depending on the various series studied (2).

In its chronic form radiation induces mucosal damage, which results in endothelial dysfunction and damage to the microvasculature with intimal fibrosis and fibrin thrombus formation in smaller arteries and arterioles, which in turn will result in ischemia, more fibrosis, and neovessel formation (3). These changes are responsible for symptoms such as diarrhea, tenesmus, urgency, pain and bleeding, which in more severe cases may require blood product transfusions. All these symptoms interfere to a greater or lesser extent with daily activities, and significantly lower patient quality of life (4).

A wide range of therapeutic options, both pharmacological and endoscopic, are currently available, which reflects the fact that studies reported in the literature to date do not show any particularly appropriate measure for each disease stage. Unfortunately, no consensus protocols exist for the treatment of this condition, hence actions must be based on the experience and equipment availability in each site. For medical therapy corticoid and 5-aminosalicylates enemas, sucralfate, metronidazole, short-chain fatty acids, antioxidants such as vitamin E, and formalin have all been used, but their usefulness seems scarce and restricted to milder cases. Surgical treatment is usually reserved for refractory patients because of its high associated morbidity and mortality (5). The ultimate goal of endoscopic treatment is bleeding control to reduce iron therapy requirements, transfusions, and hospital stays, which will result in improved quality of life. Historically, various endoscopic techniques, including Nd:YAG laser, KTP laser, heat probes, and bipolar electrocoagulation, have been used (6), but all of them have been set aside by argon plasma coagulation (APC) during the past few decades, as this technique is technically easier and more readily available.

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The potential to develop chronic radiation proctitis (CRP) and its extent depend on factors such as total dosage, radiotherapy method, radiated surface area, concomitant therapies, and patient-related factors such as prior proctocolitis, smoking, or diabetes (7). In patients who received low RT doses for a presumably mild-moderate disease scientific evidence supports the use of APC as the treatment of choice (8). However, in patients who received high doses because of more severe endoscopic and clinical involvement, as those described in the present study, the efficacy and safety of APC has been questioned. This is because, having received more radiation, the rectum would be more ischemic and less supplied with blood, hence mucosal healing would be hindered after neovessel coagulation with APC and a higher potential for complications would theoretically exist on a necrotic, more ischemic tissue (perforations, ulcers, fistulas). However, scientific evidence is presently limited on this topic, and further studies as the one reported in this issue are to be encouraged (9).

Hortelano et al. (9) publish their experience in the treatment of CRP-related rectorrhage using APC in patients who received high RT doses for the management of prostate cancer with curative intent, in an effort to establish whether this technique is effective and safe in this particular group of patients. To this end the authors performed a retrospective review of patients managed in their site with high-dose RT (defined as doses > 70 Gy) for 7 years. All patients had symptoms (CTCAE v3.0: Grade 3) and had severe endoscopic involvement (Zinicola score). They assess bleeding control based on manifestations and hemoglobin levels, as well as the development of both short-term and long-term complications. Median patient follow-up is longer than 12 months, which seems reasonable to assess treatment efficacy and potential for complications. This study shows encouraging results regarding efficacy and safety with a complete response in 77 % of patients and a partial response in 16.6 %, which represents an overall improvement in 93 % of cases. A systematic review on this subject has been recently published, which shows symptom resolution or improvement in 98 % (range 51-100 %) of 416 patients treated with APC, which seems equivalent to findings in this national study (10). It should be highlighted that most papers included in said review together discuss all CRP cases regardless of severity or administered radiation doses. Three prospective though non-controlled papers are to be underscored as they do specify patients are severely ill, with a positive response ranging from 79 % to 97 % (10). These studies, as they are heterogeneous and include limited numbers of patients, do not allow definitive conclusions on the subject. Regarding APC therapy safety in the setting of severe CRP, while there is a theoretical higher risk for perforation and ulcer post-treatment, usually requiring a greater number of longer sessions (11), the findings in this study by Hortelano et al. show an acceptable complications rate (6 %), with all events being of moderate severity and amenable to conservative measures.

Effectiveness and safety results are satisfactory though, as the authors note, the study has two important limitations, namely its retrospective nature and the relatively low number of patients included, which makes caution advisable when interpreting findings (9). The low incidence of the studied condition renders the performance of a conclusive, single-center study challenging, and shows a need for prospective, multicenter studies to combine forces in searching an appropriate treatment for CRP based on strong scientific evidence.

In recent years studies have been reported that show new endoscopic management options for CRP. Radiofrequency (12) and cryoablation stand out among these (13).

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However, their efficacy is unknown since experience is limited to small, uncontrolled series of cases.

Hyperbaric oxygen therapy (HBOT) has been used for years in the management of delayed RT complications. The patient intermittently breathes 100 % oxygen while the treatment chamber is pressurized to a value above sea-level (1 absolute atmosphere). This promotes neovascularization through hyperoxygenation of the damaged tissue, which induces healing in the damaged rectal mucosa and consequently reduced bleeding (14). In the scarce studies reported thus far HBOT seems to be a technique that achieves good results in patients with CRP refractory to other treatments, albeit evidence remains limited as yet (15).

Assuming that, despite the scant evidence available, HBOT and APC are likely safe, effective therapies, questions arise that should be answered in the upcoming future –Should we use HBOT for all patients or rather reserve it for those failing to respond to APC? If both therapies are chosen, should they be used sequentially or concomitantly? Is there a role for radiofrequency or cryoablation in these patients?

The evidence currently available does not allow our answering these questions. It is therefore necessary that prospective, randomized, multicenter studies be designed with adequate sample sizes to provide these much sought-after responses. Our view is that, in the near future, the combined use of these therapies will most likely become the option of choice to manage complex patients with severe CRP previously treated with high-dose RT. Indeed, there is much room for improvement in the management of these patients, and efforts should be made to systematize it based on a scientific evidence that remains to be demonstrated. Meanwhile, results such as those reported in the present paper suggest that, by carefully selecting candidates, we may use APC in patients previously treated with high-dose RT with good results and an acceptable complications rate.

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