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REIRRADIATION FOR UNOPERATED RECTAL CANCER AFTER PRIOR PELVIC RADIATION THERAPY: A CASE REPORT

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ABSTRACT
INTRODUCTION: *REGARDING PELVIC RECURRENCE OF UNOPERATED COLORECTAL CANCER, REIRRADIATION MAY BE AN OPTION FOR PATIENTS WHO STILL REFUSE SURGERY. COMORBIDITIES LIKE HIGH BODY-MASS-INDEX AND DIABETES HAS BEEN PROVEN TO BE UNFAVORABLE PROGNOSTIC FACTORS FOR PATIENTS WITH RECTAL CANCER. THE REPORT DESCRIBES*
CASE DESCRIPTION: *A 52 YEAR-OLD MAN KNOWN WITH TYPE 2 DIABETES MELLITUS AND DIAGNOSED IN 2012 WITH LOCALLY ADVANCED RECTAL ADENOCARCINOMA WHICH UNDERWENT NEOADJUVANT CHEMORADIOTHERAPY THAT REFUSED SURGERY. THE PATIENT ALSO REFUSED CHEMOTHERAPY REGIMENS, UNDERGOING ONLY CAPECITABINE SINGLE-AGENT THERAPY. FOLLOW-UP CT SCAN AND COLONOSCOPY IDENTIFIED LOCAL PROGRESSION AND, DUE TO PATIENT'S SURGERY REFUSAL, REIRRADIATION AND CONCURRENT CAPECITABINE BASED CHEMOTHERAPY WAS ADMINISTERED. REIRRADIATION WAS PERFORMED USING THE IMRT TECHNIQUE AND A HYPOFRACTIONATED RADIOTHERAPY REGIMEN. AT FOLLOW-UP CT SCAN A REDUCTION OF THE TUMORAL MASS WAS OBSERVED, WITH NO SIGNS OF METASTATIC DISEASE.*
CONCLUSION: *THIS CASE REPORT SUGGESTS THAT, IN VERY CAREFULLY SELECTED RECTAL CANCER PATIENTS, PELVIC RE-REIRRADIATION MIGHT BE AN OPTION FOR THOSE WHO REFUSE SURGERY.*

KEYWORDS: CANCER, RECTUM, RADIOTHERAPY, CHEMOTHERAPY, REIRRADIATION

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INTRODUCTION

Despite survival rates are continually improving, colorectal cancer (CRC) is still a major cause of cancer morbidity and mortality worldwide[4].

For locally advanced rectal cancer neoadjuvant chemoradiotherapy (NACRT)[5] and resection radicality[6] were the most important predictors for local recurrence and overall survival.[7] Although for some patients complete response has been achieved following NACRT, current guidelines strongly recommend surgery following NACRT for rectal cancer patients with locally advanced disease.[8,9] Sedentary lifestyle, western diet, obesity alongside other lifestyle and dietary risk factors for developing type 2 diabetes were associated with an increased risk of developing colorectal cancer.[10,11,12] Current literature data are mainly suggesting a positive association between these two diseases, suggesting that diabetes might be a risk factor for developing colorectal cancer.[13,14]

Herein, we report a case of a male patient diagnosed with locally advanced rectal cancer, known with multiple unfavorable prognostic factors including type 2 diabetes, who received 2 courses of radiotherapy to the pelvis, obtaining improved local control and OS, despite not undergoing radical surgery.

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CASE REPORT

A 52-year-old man known with type 2 diabetes mellitus and grade II obesity presented in April 2012 at the emergency with dyspnea, skin pallor and altered general condition and with a 3-month history of rectal bleeding. At digital rectal exam and colonoscopy (**Fig.3.A.1.**) a 6 cm x 4 cm tumor is identified in the lower rectum starting from the anal verge. Due to tumor friability a tumoral fragment detached and was sent to pathological examination which confirmed the diagnosis of a well differentiated tubular colorectal adenocarcinoma. Considering massive blood loss (haemoglobin (HGB) = 4.2 g/dl) inferior mesenteric artery embolization and multiple blood transfusions were performed, leading to an improvement of patients general condition and blood tests (HGB=10.4 g/dl).

Head-thorax-abdomen and pelvis computed tomography (CT) scan staging identified an inferior rectum locally invasive tumoral mass (**Fig.3.B.1.**) with bilateral internal iliac adenopathies. Given these results the disease was, based on American Joint Commission on Cancer (AJCC)[15], stage IIIB (T3N1M0), therefore NACRT followed by radical surgery was the proposed treatment.

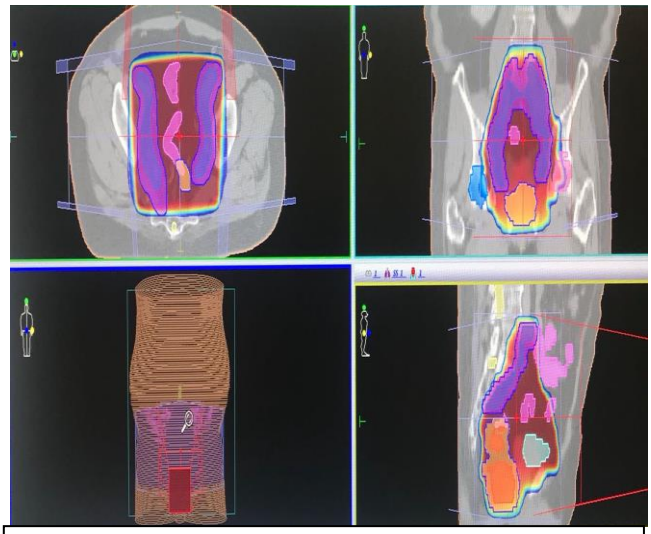

Fig.1 Initial pelvic radiotherapy using a 3D conformal "4-field-box" technique

Radiotherapy was performed using a "4-field-box" (**Fig.1**) 3D conformal technique to a total dose of 50 Grays (Gy) for a target volume including regional lymphnodes using a conventional 2 Gy fractionation schedule. During radiotherapy fluoropyrimidine-based chemotherapy was administered with Capecitabine 825mg/m2 twice daily, 5 days/week for 5 weeks. Follow-up CT scan and rectoscopy showed stationary disease, with no pelvic enlarged lymphnodes. Although radical surgery was proposed, the patient refused it, therefore the multidisciplinary tumor board for salvage 6 cycles of chemotherapy type CAPEOX with Oxaliplatin 130mg/m2 day 1 and Capecitabine 1250 mg/m2 twice daily days 1-14 every 3 weeks.

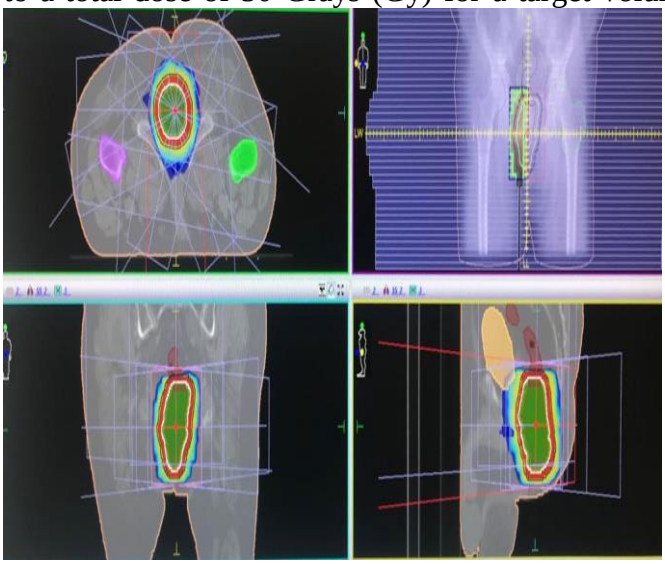

Fig.2 IMRT reirradiation treatment plan

[15] Colon and Rectum. In:Compton CC., Byrd DR., Garcia-Aguilar J., Kurtzman SH., Olawaiye A., Washington MK. (eds.) AJCC Cancer staging atlas, 2nd Ed. New York: Springer; 2012

The patient refuses Oxaliplatin treatment, therefore Capecitabine monochemotherapy is administered for six months.

Following six months of chemotherapy the patient presents with rectal bleeding, inability to completely empty the bowel and constipation, surgical and imaging exams (**Fig.3.A.2. and B.2.**) confirming a local progression of the disease. Surgery is proposed, but the patient refuses it for the second time therefore reirradiation is proposed. Intensity modulated radiotherapy (IMRT)(**Fig.2)** has been performed irradiating current tumor extension to a total dose of 36 Gy in 12 fractions using a 3 Gy/day fractionation schedule, administering by simultaneous integrated boost technique a radiation dose of 39 Gy for initial tumor extension using a 3.25 Gy/fraction schedule. During radiotherapy concurrent Capecitabine chemotherapy 825mg/m2 twice daily, 5 days/week was administered. All symptoms were palliated after the starting from the 2nd treatment week, whilst patient tolerance was good, the only reported side effect being grade 3 proctitits and grade 2 rectalgia. Following chemoradiotherapy, Capecitabine monochemotherapy 1250 mg/m2 twice daily days 1-14 every 3 weeks was administered for eight months. At follow-up thorax-abdomen-pelvis CT scan (**Fig.3.B.3.**) asymmetrical parietal thickening of the lower rectum wall, with appearance in mild regression towards the previous CT exam was identified. Colonoscopy confirms the reduction of the lower rectum tumoral mass (**Fig.3.A.3.**).

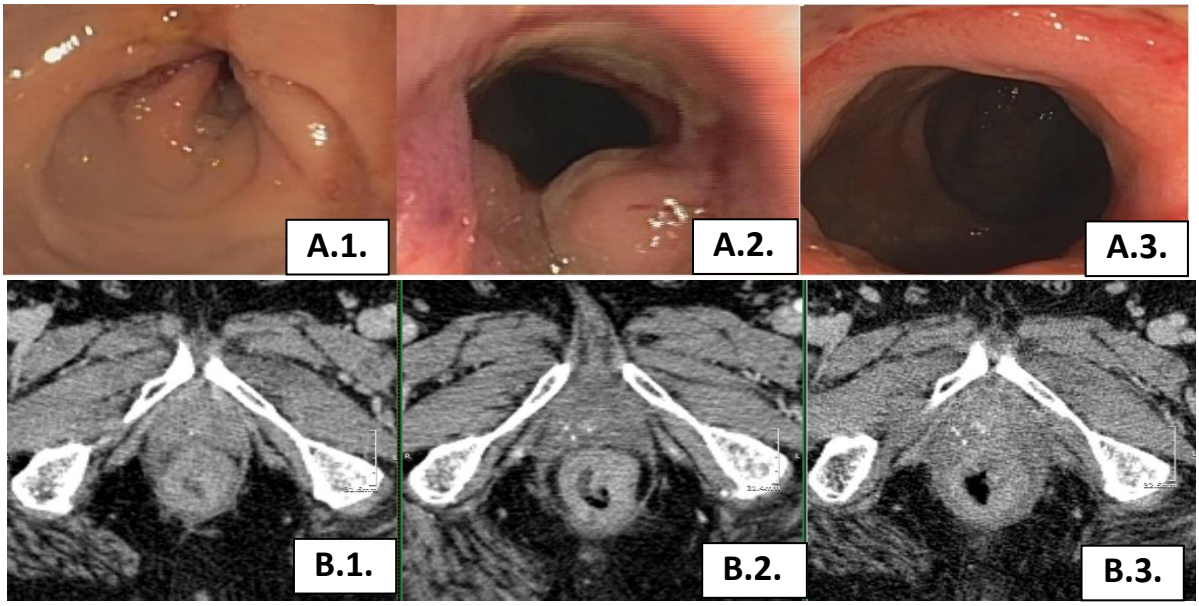

Fig.3. Colonoscopy (A.) and CT scan (B.) images at diagnosis (1.), relapse (2.) and at latest posttreatment follow-up (3.)

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DISCUSSION

Current literature data strongly suggest a direct link between diabetes mellitus and colorectal cancer, most of these studies taking into account that diabetes mellitus might be considered an unfavorable prognostic factor for patients who develop colorectal cancer. In 2005 *Larson SC. et al.*[14] performed a metanalysis of fifteen studies with the purpose of finding a link between colorectal cancer and diabetes mellitus. Their results strongly support a connection between these two diseases in both women and men suggesting that hyperinsulinemia or insulin resistance might take part at the carcinogenetic process of colorectal cancer. Literature data suggest multiple links between diabetes mellitus and colorectal cancer. Therefore patient lifestyle focused studies suggest that both types 2 diabetes and colorectal cancer share risk factors like high body-mass-index (BMI) and sedentary lifestyle.[13,16]Currently, although there are studies that consider diabetes mellitus an independent risk factor for colorectal cancer[17], most epidemiological research data suggest that there are multiple connections between these two diseases which can be explained by certain biological processes like high levels of circulating C-peptide[18,19], insulin-like growth factor (IGF)-1[20,21] and insulin[22]. Epidemiological data identified that for cancer patients comorbidities increase the need of a more complex therapeutic management, also decreasing disease free survival (DFS) and overall survival (OS) parameters.[23,24] These data are not only related to diabetes mellitus, but also to high body-mass-index, which proved to be associated with an increased mortality rate compared to the normal weight category.[25] Regarding rectal cancer patients that didn't undergo surgery following neoadjuvant chemoradiotherapy, *Lim et al.*[26] identified a progression-free-survival (PFS) of 65

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months for the complete response (CR) patients, compared to 15 months for the partial response (PR) ones. The same study identified that for stage T3 rectal cancer patients the median PFS was 28 months. T stage and clinical response were both considered predictors of PFS, but also that medical comorbidities and advanced age are unfavorable prognostic factors, reducing median overall-survival (OS) in rectal cancer patients who don't undergo surgery from 64 months to 27.5 months. Several literature data regarding rectal cancer reported high local recurrence rate even for complete responders not submitted for surgery within 3.7 to 8.8 months from chemoradiotherapy. Also, the same data suggest that adding brachytherapy to chemoradiotherapy did not improve PFS and OS.[27,28] Regarding local recurrent rectal cancer that was previously irradiated multiple literature data suggest that reirradiation up to 30-40 Gy might be safe for palliation in resectable tumors.[29,30,31] Prior studies regarding rectal cancer reirradiation[30,32,33], in which different radiotherapy schedules were used, concluded that the retreatment dose, and not the cumulative radiation dose, plays an important role for the OS rates of these patients. Therefore, by using a median cumulative dose of more than 30 Gy, OS rates of more than 20 months were achieved.[34] Although in most of these studies accelerated hyperfractionation radiation regimens were used, only *Nget al.*[33] published in 2013 the results of a study evaluating a once-daily reirradiation regimen for rectal cancer patients. This study concluded that reirradiation resulted in an 88% symptomatic response, but with poor OS rates of just 15 months for patients that didn't undergo radical surgery. The patient in this case report had multiple unfavorable individual prognostic factors like diabetes mellitus, dislipidemia and cardiac insufficiency. Besides that, more significant negative prognostic factors related to treatment were present such as refusing surgery and undergoing monochemotherapy with Capecitabine as systemic treatment. From our knowledge this is the only case of reirradiation of a patient with local relapse of rectal cancer without undergoing surgery or polichemotherapy regimens. PFS for our patient was comparable to previously reported data, but OS proves to be

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higher than in these studies. Although there were data that reported even a third reirradiation[35], from our knowledge this is the first case describing a hypofractionated regimen of reirradiation for a recurrent rectal cancer. Current reported data suggested increased grade 3 and 4 gastrointestinal toxicity, but also lumbosacral plexopathy following the second reirradiation, but this is not applicable to our patient, probably due to the reirradiation of a target volume limited to the relapsed tumor and not of the whole pelvis.

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