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Identification of Predictive Factors for Pathologic Complete Response in Rectal Cancer Patients Undergoing Neoadjuvant Treatment: A Retrospective Study

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Abbreviations:
CRC: Colorectal cancer;
LARC: locally advanced rectal cancer;
pCR: pathologic complete response;
NARCT: neoadjuvant chemoradiotherapy;
CT: computer tomography;
AJCC: American Joint Committee on Cancer;
EBRT: external beam radiotherapy;
IMRT: intensity modulated radiation therapy;
LINAC: linear accelerator;
VMAT: volumetric modulated arc therapy;
ROC: Receiver operating characteristic.

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Rezumat

Identificarea factorilor predictivi pentru răspunsul patologic complet după tratamentul neoadjuvant la pacienții cu cancer de rect - un studiu retrospectiv

Introducere: Cancerul colorectal este o afecțiune severă, cu cancerul rectal reprezentând treizeci la sută din toate cazurile. Pentru pacienții diagnosticați cu cancer rectal, chimioradioterapia neoadjuvantă este frecvent necesară ca o consecință a gradului extensiei tumorale la momentul prezentării la medic. Cu toate acestea, pentru o anumită populație de pacienți, chimioradioterapia neoadjuvantă poate avea drept rezultat un răspuns complet, ceea ce ar transforma intervenția chirurgicală definitivă într-o opțiune terpaeutică nejustificată.
Metode: Pentru a identifica factorii predictivi pentru răspunsul clinic sau patologic complet, am efectuat un studiu retrospectiv asupra a 231 de pacienți diagnosticați cu cancer rectal local avansat care au efectuat chimioradioterapie neoadjuvantă.
Rezultate: Rezultatele obținute indică faptul că anumite caracteristici tumorale rămân factorii predictivi principali pentru răspunsul la tratament la pacienții cu cancer rectal. În mod particular, am constatat că un răspuns patologic complet este mai

probabil la pacienții cu boală în stadiile I/II în comparație cu cei aflați în stadiile III/IV. Cu toate acestea, nu am identificat nicio asociere semnificativă statistic între caracteristicile radioterapiei (cum ar fi fracționarea, tehnica de tratament sau doza totală) şi frecvența răspunsului complet.
Concluzii: În concluzie, studiul nostru evidențiază importanța stadiului tumoral ca predictor al răspunsului patologic complet după chimioradioterapia neoadjuvantă pentru pacienții cu cancer rectal. Alți factori clinici şi patologici, cum ar fi mărimea tumorii, pot fi, de asemenea, predictori importanți ai răspunsului la tratament şi ar trebui explorați în studii viitoare

Cuvinte cheie: cancer colorectal, raspuns complet, tratament neoadjuvant, radioterapie, chirurgie

Abstract
Background: Colorectal cancer is a serious illness, with rectal cancer accounting for thirty percent of all cases. For patients diagnosed with rectal cancer, neoadjuvant downstaging chemoradiotherapy is often necessary due to advanced disease at presentation. However, for certain patients, neoadjuvant chemotherapy can result in a complete response, leading to the possibility of overtreatment during subsequent definitive surgery.
Methods: In order to identify predictors for clinical or pathologic complete response, we conducted a retrospective study on 231 patients diagnosed with locally advanced rectal cancer who underwent neoadjuvant treatment.
Results: Our results indicate that tumor characteristics remain the primary predictive factors for treatment response in rectal cancer patients. Specifically, we found that a complete pathologic response was more likely in patients with stage I/II disease compared to stage III/IV. However, we did not identify any statistically significant associations between radiotherapy characteristics (such as fractionation, treatment technique or total dose) and complete response rates.
Conclusions: In conclusion, our study highlights the importance of tumor stage in predicting pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer patients. Other clinical and pathologic factors, such as tumor size, may also be important predictors of treatment response and should be explored in future studies.

Key words: colorectal cancer, complete response, neoadjuvant therapy, radiotherapy, surgery

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide with an incidence of 1.9 million cases and it is responsible for 0.94 million deaths in 2020. The number of new cases of CRC in Romania in 2020 was 7 885, occupying the 4th place in incidence and a mortality rate of 4 302 (1,2).

Whilst the highest incidence rates are reported in developed countries, increasing incidence was reported in developing countries (3). Dietary habits, responsible not only for cardiovascular disorders (4-6), a large number of epidemiological data linked co-existing pathologies, especially type 2 diabetes (7-9), contribute to the development and to treatment resistance of colorectal cancer (10,11). Surgery remains the curative treatment for colorectal cancer (11), even in the oligometastatic setting or for potential oncological treatments side effects (12).

For locally advanced rectal cancer (LARC) the standard of care consists of neoadjuvant radiotherapy either alone (short course), or with concurrent 5-FU or oral Capecitabine

(long course) followed by surgery the following week (12,13), or 6-10 weeks later (14). For the long course concurrent chemoradiotherapy regimen, pathologic complete response (pCR) was reported to proportionally increase with the total radiation dose (15-18). Pathologic complete response is associated with potential cure and offers the possibility of surgical excision in an organ preservation approach. the (10,17,19). Considering the uncertainty surrounding the rectal cancer predictors of sensitivity to neoadjuvant chemoradiotherapy (NACRT), we aimed to study patient, tumour and treatment related characteristics linked to pCR in rectal cancer.

Material and Method

Between January 2017 and December 2020, 231 consecutive patients diagnosed with rectal cancer were treated at Oncofort Private Hospital, Bucharest, Romania. Previous to NACRT all patients underwent complete biological and oncological evaluation through complete blood count, liver and renal functional tests, full colonoscopy, thorax-abdomen-pelvis computed tomography (CT) and pelvic magnetic resonance imaging (MRI). For tumoral staging, 8th American Joint Committee on Cancer (AJCC) Cancer Staging Manual was used (20). After diagnostic work-up, all cases were discussed in an oncological multidisciplinary board for treatment decision. From these, 87 patients received preoperative treatment consisting either of short-course radiotherapy or of long-course radiotherapy with concurrent Capecitabine, corresponding dose 2500 mg/day. The dose was adjusted to the corresponding body surface area using Du Bois formula (21). Patients had their creatinine clearance calculated with Cockroft-Gault formula (22). External beam radiotherapy (EBRT) was administered using a 6 MV linear accelerator (LINAC), targeting the primary tumour and regional lymph nodes using Intensity Modulated (IMRT) treatment technique or Volumetric Modulated Arc Therapy (VMAT). For each patient we collected age, gender, employed radiation therapy technique, dose, type of boost, time to surgery and chemotherapy type. Variations in preoperative treatment were related to fractionation schedule and total radiation dose. Following NACRT, all patients underwent clinical re-evaluation by colonoscopy, thorax-abdominal CT scan and pelvic MRI. After surgery, pathology report data, such as tumor stage and examined lymph nodes status were collected. Complete pathologic response was defined as ypT0 ypN0 after surgical excision, ypT0 for tumor bed tissue sampling after NARCT and any ypT>0 or ypN>0 was defined as incomplete response We chose the cut-off age of 74. This value corresponds to the Romanian life expectancy, both sexes.

We have used Pearson Chi-squared and one way ANOVA tests to check for differences between groups. The Receiver operating characteristic (ROC) curve, with De long et al. (1988) method, was used to analyze the sensitivity of irradiation dose and age of patients on the response after treatment. The Youden Index is used to determine the cut-off point. The Logit and Probit models were used to analyze the impact of certain predictors on the response type and to compute ODD ratios.

Figures and data analysis was done in Data analysis was performed in Microsoft EXCEL, IBM SPSS v.21, Medcalc and R Studio (23-26). For statistical significance we have chosen p-value<0.05. The 95% confidence interval is given when appropriate.

Results

Eighty-two patients have been eligible for analysis and the average age was 63 years (range 30-87). The males represented 58.5 % and the females 41.5%. For half of the sample (48.8%), the tumor was located in the lower rectum, while for the 43.9 %, in the middle rectum. Only 7.3 % of the patients had upper rectum location. One can see the share of the patients by TNM stage grouping in *Fig. 1* and further details are presented in *Table 1.*

Most patients had either stage II (41.5%) or III (35.4%) while 4 patients had stage IV (6.1%).

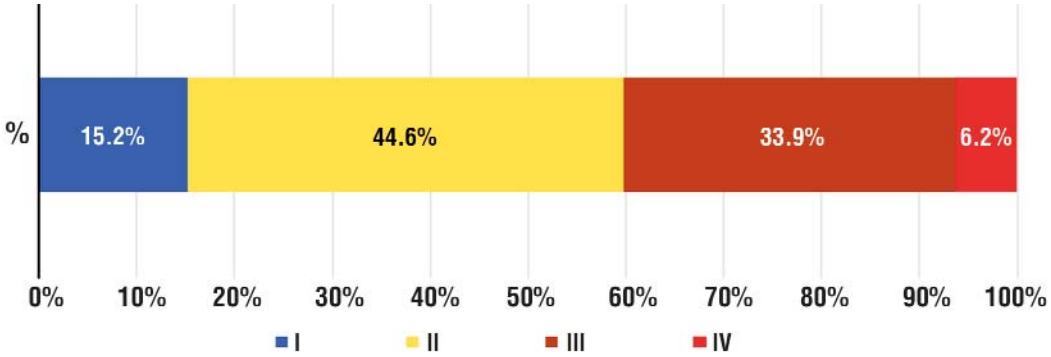


Figure 1. The share of patients by tumor stage.

Table 1. Patient population characteristics and treatment parameters stratified by pathologic complete response to neoadjuvant chemoradiotherapy. 1 – ANOVA testing, 2 – Pearson Chi-square. (SD-standard deviation, IMRT – intensity modulated radiation therapy, VMAT – volumetric modulated arc therapy, SIB – simultaneous integrated boost, EQD2 – Equivalent Dose in 2 Gy Fractions, BED – biological equivalent dose).

Feature	Incomplete response (N=61)	Complete response (N=21)	Total (N=82)	p-value
Mean age (range)	62.9 (37-87)	63 (35-81)	62.93 (35-87)	0.069 (1)
Tumor location				0.194 (2)
Lower rectum	27 (44.3%)	13 (61.9%)	40 (48.8%)	
Middle rectum	28 (45.9%)	8 (38.1%)	36 (43.9.0%)	
Upper rectum	6 (9.8%)	0 (0.0%)	6 (7.3%)	
T stage				0.003 (2)
T2	10 (16.4%)	11 (52.4%)	21 (25.6%)	
T3	46 (75.4%)	10 (47.6%)	56 (68.3%)	
T4	5 (8.2%)	0 (0.0%)	5 (6.1%)	
N stage				0.047 (2)
N0	26 (42.6%)	15 (71.4%)	41 (50.0%)	
N1	28 (45.9%)	6 (28.6%)	34 (41.5%)	
N2	7 (11.5%)	0 (0.0%)	7 (8.5%)	
Grade				0.198 (2)
1	10 (16.4%)	6 (28.6%)	16 (19.5%)	
2	41 (67.2%)	15 (71.4%)	56 (68.3%)	
3	9 (14.8%)	0 (0.0%)	9 (11.0%)	
4	1 (1.6%)	0 (0.0%)	1 (1.2%)	
Technique				0.129
IMRT	19 (31.1%)	9 (42.9%)	28 (34.1%)	
VMAT	42 (68.9%)	12 (57.1%)	54 (65.9%)	
Long/short course				
Long	56 (91.8%)	21 (100.0%)	77 (93.9%)	0.176 (2)
Short	5 (8.2%)	0 (0.0%)	5 (6.1%)	
Boost				
No	45 (73.8%)	15 (71.4%)	60 (73.2%)	0.767 (2)
Yes	16 (26.2%)	6 (28.6%)	22 (26.8%)	
SIB			0.835 (2)	
No	45 (73.8%)	15 (71.4%)	60 (73.2%)	
Yes	16 (26.2%)	6 (28.6%)	22 (26.8%)	
Stage				0.005 (2)
I	6 (9.8%)	8 (38.1%)	14 (17.1%)	
II	24 (39.3%)	10 (47.6%)	34 (41.5%)	
III	26 (42.6%)	3 (14.3%)	29 (35.4%)	
IV	5 (8.2%)	0 (0.0%)	5 (6.1%)	
Dose mean (range) EQD2	45.2 (30-50.4) Gy	46.76 (45-50.4) Gy	45.625 (30-50.4) Gy	0.206 (1)
BED (Gy)				0.135 (2)
< 40	6 (9.8%)	0 (0.0%)	6 (7.3%)	
≥ 40 Gy	55 (90.2%)	21 (100.0%)	76 (92.7%)	
Time until surgery				0.117 (2)
> 4 weeks	38 (62.3%)	17 (81.0%)	55 (67.1%)	
≤ 4 weeks	23 (37.7%)	4 (19.0%)	27 (32.9%)	

Two types of irradiation techniques were applied. More than half of the patients were treated using VMAT (65.9%) while the rest were treated using IMRT (34.1%). More details about technique of irradiation and principal sub-categories of patients are available in the *Fig. 2*. All studies sub-groups are homogenous regarding the irradiation technique applied. There is no statistical difference (Chi-Square statistics, p-value > 0.05) between stages, gender or between main age-groups. Regarding boost, 73.2% benefited from a sequential boost irradiation while 26.8% received it in the form of simultaneous integrated boost (SIB). The majority of the patients received a long course irradiation regimen (93.9%) and only 6.1 % a short-course. Most patients that had a complete pathologic response had the surgery after more than 4 weeks from neoadjuvant treatment (81%).

For patients grouped by stage I/II vs III/IV, using Pearson's Chi-squared test we found that a complete pathologic response was more likely in patients with stage I/II, compared to stage III/IV (χ^2=8.59, p=0.007 with Yates' continuity correction). Based on the odds ratio, the odds of patients with complete pathologic response were 16.5 (95% CI = [2.81, 64.85]) times more likely if they had stage I/II, than if they had stage III/IV. For patients without any enlarged lymph nodes, a complete pathologic response was more likely than in patients with nodal disease (χ^2=5.19, p=0.23]). For stages III/IV no factors influencing complete response were identified. For patients without nodal disease (N0), neither sequential, nor simultaneous integrated boost (SIB) didn't improve the outcome (χ^2=0.51, p=0.47). These results were similar for stage I/II cancer patients (χ^2=0.37, p=0.54). Regarding post-radiation therapy surgery (in weeks), 27 patients had the procedure 4 weeks after RT completion, 33 at 8 weeks and the rest of patients more than 8 weeks. In the subgroup of patients with highest pCR (stage I vs stage II), no other treatment features nor patient or tumour characteristics were associated with a higher probability of pCR (*Table 2*).

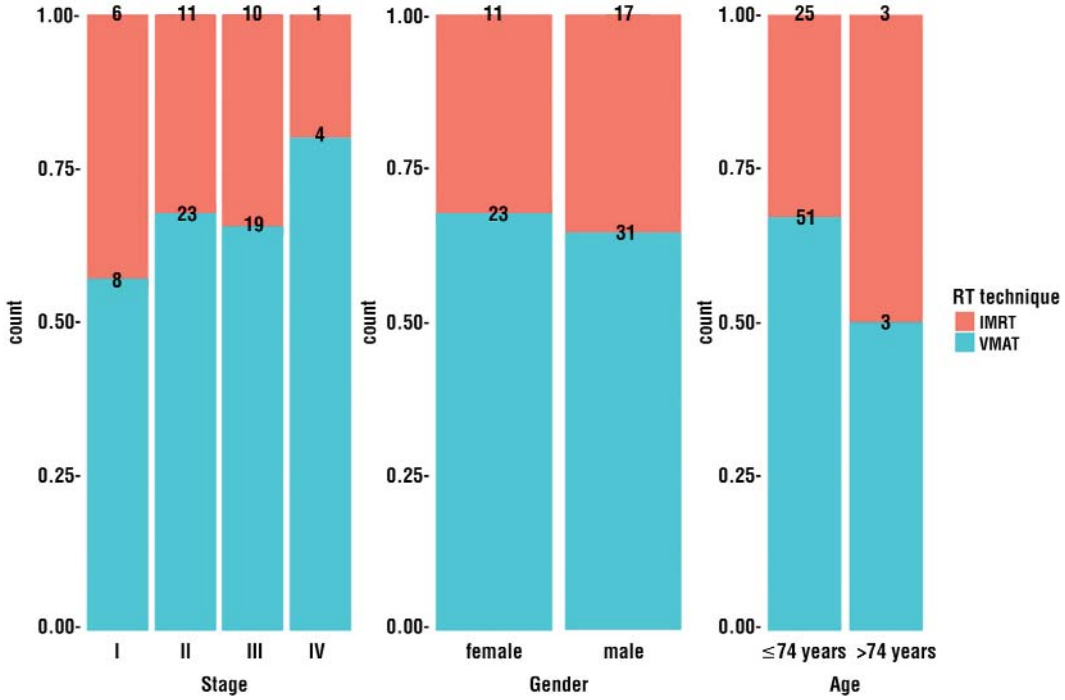


Figure 2. Proportion of patients by applied irradiation technique, gender, age-group and stage of disease.

Table 2. Complete response controlled by stage I or II (1 - ANOVA, 2 - Pearson Chi-square, NA - not available, EQD2 – Equivalent Dose in 2 Gy fractions).

Feature	Incomplete response (N=30)	Complete response (N=18)	Total (N=48)	p-value
Mean age (range)	64.233 (37-87)	61.9 (35-81)	63.35 (35-87)	0.469 (1)
Tumor location				
Lower rectum	11 (36.7%)	10 (55.6%)	21 (43.8%)	0.295 (2)
Middle rectum	17 (56.7%)	8 (44.4%)	25 (52.1%)	
Upper rectum	2 (6.7%)	0 (0.0%)	2 (4.2%)	
Long/short course				
Long	28 (93.3%)	18 (100.0%)	46 (95.8%)	0.263 (2)
Short	2 (6.7%)	0 (0.0%)	2 (4.2%)	
Boost				
No	10 (33.3%)	5 (27.8%)	15 (31.2%)	0.688 (2)
Yes	20 (66.7%)	13 (72.2%)	33 (68.8%)	
SIB				
No	23 (76.7%)	12 (66.7%)	35 (72.9%)	0.450 (2)
Yes	7 (23.3%)	6 (33.3%)	13 (27.1%)	
Grade (1 NA)				
1	7 (23.3%)	6 (33.3%)	13 (27.1%)	0.242 (2)
2	19 (63.3%)	12 (66.7%)	31 (64.6%)	
3	4 (13.3%)	0 (0.0%)	4 (8.3%)	
Dose mean (range)	45.747 (31.25-50.4)	45-50.4	31.25-50.4	0.391 (1)
Time until surgery/biopsy				
> 4 weeks	20 (66.7%)	14 (77.8%)	34 (70.8%)	0.412 (2)
≤ 4 weeks	10 (33.3%)	4 (22.2%)	14 (29.2%)	

Although there are no visible differences, we enhanced the analysis and we searched for particular groups of patients to find predictors for a better response.

The ROC curve analysis reveals that the dose value for the IMRT technique has no significant (p-value=0.405) predictive capacity to discriminate between complete and partial response of patients. Meanwhile, in the VMAT case, the area under the curve (AUC) significantly differs from the reference value (0.5) and suggest that irradiation dose value has significant impact in achieving a complete response vs a partial response. The Youden Index, identify a value of 45 Gy as equilibrium point (cut-off) between sensitivity and specificity. In this point the values are 84.6% for Sensitivity and 54.7% for specificity. When the dose increases the specificity increases, but sensitivity decreases. A dose increment associated an increase in specificity at the expense of sensitivity.

One can see in the *Fig. 3* that in the case of VMAT, higher irradiation doses increase the probability of complete response up to 60%, while low dose, below 40 Gy, suggest smaller impact on the probability to achieve a complete response. In the case of IMRT technique, higher dose of irradiation rather decreases the chance of having a complete response. One can see on the right side of *Fig. 4*, that doses around 45-46 Gy associates a 40% chance of complete response, while doses around 50 Gy, associate less than a half chances of complete response.

We performed the same analysis for age, as continuous variable, without significance.

Modelling the probability of achieving a complete response via binary logistic regression, we achieve heterogenous results. One can observe in the IMRT column from *Table 3*, that predictors have no statistically significant impact on the result. On the VMAT branch, the irradiation dose, gender and patient TNM stage have risks lower than 0.1 and 0.05 respectively, at Chi-Square test applied in the binary regression modelling.

Then, a patient with treated with VMAT

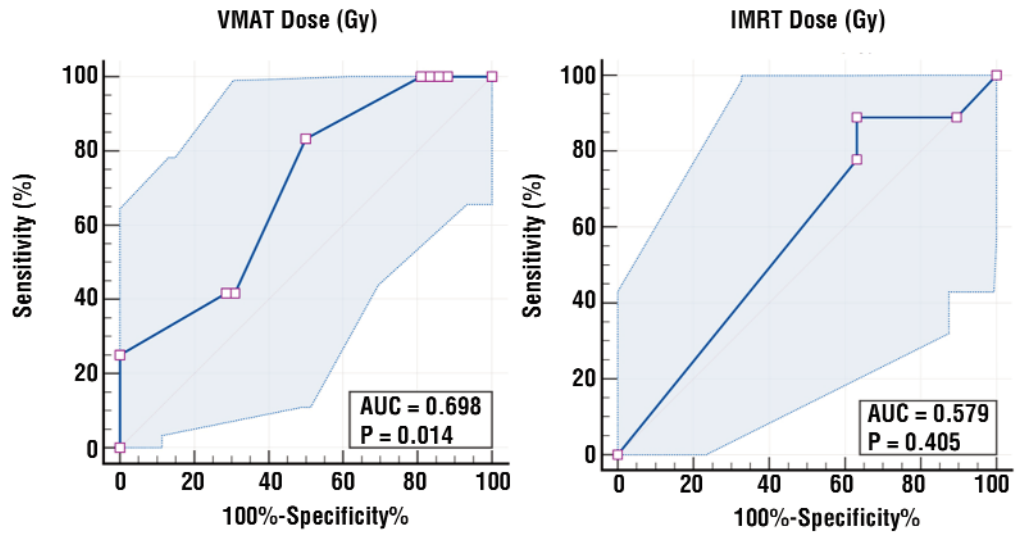


Figure 3. ROC curve results with 95% confidence limits, for the impact of dose and irradiation technique on the response of patients (captures are based on the Medcalc outputs).

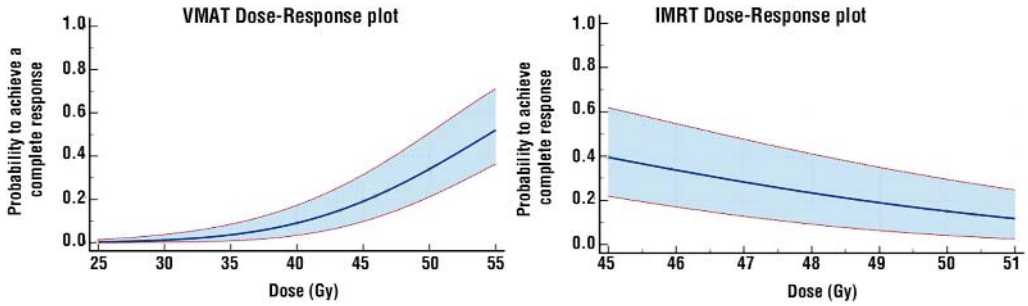


Figure 4. The Probit estimated probability and 95% bands for dose-response analysis by irradiation technique.

have in mean additional 3.76% chance to achieve a complete response for each supplementary 0.1 Gy dose. Patients in a stage greater than I have 86% smaller chances (OR=0.139, 95% CI [0.022-0.895]) to achieve a complete response. Overall, the regression

Table 3. Possible predictors of complete response by irradiation technique.

Feature	IMRT OR(95% CI)	VMAT OR(95% CI)
Dose(Gy)	0.710(0.418-1.204)	1.376(0.942-2.010)*
SIB (ref=0)	1.821(0.108-30.526)	1.421(0.242-8.335)
Stage (ref=Stage I) 0=Stage I; 1=Stage>1	0.181 (0.012-2.788)	0.139(0.022-0.895)**
Gender (ref=female)	0.351(0.052-2.388)	0.163(0.030-0.909)**
Sequential boost (ref=no sequential boost)	1.235(0.059-25.553)	5.310(0.394-71.629)
Constant	-	-
Percentage of cases correct classified with the model	71.4%	83.3%
Nagelkerke R Square	0.237	0.389

*p-value <0.1; **p-value <0.05

model classifies correctly 83.3% of total cases, these values suggesting an acceptable threshold. Furthermore, male patients have in mean 83.7% less chances to achieve a complete response by comparison with females, under the hypothesis to maintain other factors constant.

In the case of IMRT technique the results are not satisfactory. None of the coefficient is statistically significant, and the model classify correctly only 71.4% of total cases.

Discussion

Rectal cancer is the most common gastrointestinal tract cancer thus screening is available (27). Therefore, like in other digestive tract tumours it is necessary to have a good knowledge of the local neoplasms that can arise and the exhaustive local pathology. In our study on rectal cancer patients undergoing neoadjuvant treatment, we aimed to identify predictive factors for pathologic complete response, a complex process that involves multiple factors and requires a personalized approach to treatment. By identifying predictive factors for pathologic complete response in rectal cancer patients, our study aims to contribute to a growing body of research aimed at improving treatment efficacy and patient outcomes in complex medical conditions. Current literature data are inconsistent regarding the role of the gender in predicting the response to neoadjuvant chemoradiotherapy in LARC. Recently published data failed to identify gender as a pCR predictive factor for LARC undergoing neoadjuvant chemotherapy (28, 29), in contradiction to previously published data (36) that considered male gender to be associated with higher rates of pCR. In our study gender was not found to be a predictive factor, in the pCR patient population 66% were males, and 34% females. Age is also one of the patient characteristics considered a predictive factor for pCR in LARC patients.

Regarding tumour characteristics, few published literature data support the differentiation grade as a pCR predictive factor for NACRT of LARC (29–31). Considering the results of these studies, well and moderately differentiated rectal tumours were associated with higher rates of pCR. In our study, 87.8% of the patients were diagnosed with low-grade (G1-G2) rectal cancer. As presented in *Table 2*, from the patients with pCR included in our study, none was initially diagnosed with high-grade (G3-G4) differentiation grade. Regarding tumour characteristics, the tumoral stage confirmed its main roles as prognostic and predictive factor. There is also a lack of consistent literature data regarding this tumour characteristic, most studies focusing on stage III or II cancer patients. Our study included rectal cancer patients with stages I-IV that had NACRT, and found that the highest pCR rates were identified for stage I/II or N0 rectal cancer patients undergoing NACRT.

No literature data regarding tumour location as a pCR predictive factor were found following literature review. In our study, we found that the highest pCR rates following NACRT were identified for lower and medium rectal tumours, albeit not statistically significant ($p=0.192$). On closer analysis on patients which had stage I vs II, no other feature associated a higher propensity for pCR (*Table 2*).

Regarding post-radiation therapy surgery or biopsy timing our findings were that patients for which the procedure was done at eight weeks were more likely to obtain a complete pathologic response than those that had a longer/shorter timing.

In our study, the use of VMAT technique showed similar results to classic IMRT. In our study, the use of VMAT technique led to an additional 3.76% chance to achieve a complete response for each supplementary 0.1 Gy dose. Regarding total radiation dose administered to the target volume, in most studies this parameter ranged from 45 up to 50 Gy. Increasing the total radiation dose by sequential boost or simultaneous integrated boost was considered to increase the pCR rates in rectal cancer patients undergoing NACRT (36). Our study failed to confirm these data, but found that if a radiotherapy is scheduled, it should be administered sequentially and not

simultaneously in order to increase the chance of a pCR, contradicting previous published data that consider neoadjuvant treatment prolongation as a negative prognostic factor for pCR.

We created a classification model for patients that undergo radiation-therapy with VMAT technique and we plan to improve and validate the model with subsequent cases.

The size of our sample was limited and to improve the prediction model for complete response, a larger set of patients would be necessary. Due to retrospective nature of our study, we can't exclude the corresponding biases and we would suggest that a meta-analysis of similar studies to be conducted to pool all the possible parameters associated with complete pathologic response.

Conclusions

This is a retrospective study focusing on rectal cancer patients undergoing neo-adjuvant chemoradiotherapy and seeking to identify predictive factors for pCR. Tumour characteristics, especially tumour and lymph node status, and surgical/rebiopsy timing were the only ones statistically linked to the rates of pCR. Other, factors related to tumour (e.g. lower and middle rectal tumours, low differentiation grade), patient (e.g. male gender, age > 61 years) and treatment characteristics (e.g. long course radiotherapy, sequential administration of a radiation boost), although not statistically significant, were linked to an increase in the rates of pCR for rectal cancer patients undergoing NACRT. Although intensively debated, the role of chemoradiotherapy alone for locally advanced rectal cancer patients with complete pathologic response remains unclear. Our study's results should be embedded to previously published data as a necessary update for offering the patients personalized treatment management. Chemo-radiotherapy as unique treatment for rectal cancer patients with a complete pathologic response remains to be determined.

Conflicts of Interest

The authors declare no conflict of interest.

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Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Oncofort Hospital GRAL Medical (no.2348/ 23.02.2022). Informed consent was obtained from all subjects involved in the study.

Acknowledgments

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