



High-resolution anoscopy predictive modeling of anal canal cancer response after definitive chemoradiotherapy in COVID19 era

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ABSTRACT

Purpose: To develop a predictive index model, integrating both clinical and high-resolution anoscopy (HRA) features to further personalize the decision making process in anal canal carcinoma in COVID19 era.

Methods and materials: We assess HRA parameters after definitive chemoradiotherapy in patients with anal canal malignant lesions.

Results: HRA features could be important to assess the effect of CRT and a risk stratification system should be introduced in clinical practice to better allocate therapeutic interventions.

Conclusion: To our knowledge this is the first proposal for HRA findings in anal canal cancer after definitive CRT. We believe that a risk score can be useful to estimate the risk of treatment failure (in term of persistence disease and/or recurrence) and its clinical relevance should not to be underestimated.

Introduction

Anal canal cancer is a rare malignancy, accounting an estimated 50,865 new cases and 19,293 cancer deaths worldwide in 2020 [1]. Definitive concurrent chemoradiotherapy (CRT) is the standard primary treatment for patients with non-metastatic anal canal cancer [2]. Salvage radical surgery with abdominal perineal resection (APR) is reserved in case of local recurrence or disease persistence [2]. Both higher tumor (T) stage and higher nodal (N) stage at diagnosis are an important determinant of prognosis. The success of primary CRT is highly variable. In general, time to complete regression ranges from 2 weeks to 36 weeks, but anal canal carcinoma can take up to 72 weeks to disappear [3–6]. In this context, the right identification of CRT response is paramount to patient's management. At present, following definitive CRT of non-metastatic anal canal cancer, the follow-up treatment recommendations include (i) inguinal node palpation, digital rectal exploration and anoscopic evaluation every 3–6 months; (ii) annual chest/abdominal/pelvic computed tomography (CT) and pelvic magnetic resonance imaging (MRI) with contrast [2]. According to Response Evaluation Criteria in Solid Tumours (RECIST criteria), CRT response is mainly classified as complete response (total disappearance of tumor

and any pathological lymph nodes), persistent disease (including partial response and stable disease) or progressive disease [7]. In considering alternative follow-up clinical programs, especially for late responders to CRT, the most pressing challenge is an accurate and reliable post-CRT mechanism for predicting whether complete response can be achieved. The utility of high-resolution anoscopy (HRA) as surveillance tools to predict persistent or recurrent disease has not been examined extensively, yet. Ideally, any predictive modeling would be accurate in the identification of clinical response and have wide applicability. The goal of this research project is to develop a reliable model, comprised of HRA features and clinical characteristics, for predicting the outcome of primary CRT in patients with anal canal carcinoma. We hope to provide a first step towards personalized care in anal canal oncologic field.

Material and method

Study population

Patients will be accrued at the Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome. Written informed consent will be obtained from all patients before the initiation of

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therapy. Eligible patients will be those with a primary histologically proven squamous cell carcinoma of the anal canal without evidence of distant metastases at diagnosis. Exclusion criteria will include: (i) evidence of contraindications to MRI exam (pacemaker, cochlear implant) and/or high-resolution anoscopy; (ii) previous addominopelvic RT; (iii) synchronous tumors; (iv) history of neurologic or psychiatric disorders; (v) contraindication to concomitant chemotherapy (cardiovascular disease). Preoperative clinical and radiological evaluation will include complete physical examination and digital rectal exploration, HRA with assessment of HPV-status, pelvic diffusion-weighted (DW)-MRI and total body contrast-enhanced CT scan. Gynecological examination will be performed in female patients. All the procedures will be carried out by the same radiation/surgical oncology team and the DW-MRI/CT images will be all reviewed by the same dedicated radiologist. HRA procedure will be performed to evaluate potential features able to predict treatment response.

Treatment plan

All patients will be treated with a definitive concurrent CRT. Radiotherapy will be delivered via intensity modulated technique (IMRT) at a dose of 45 Gy (1.8 Gy per fraction) to the whole pelvis plus 5.4/14.4 Gy (1.8 Gy per fraction) to the tumor volume with 6 to 15 MV energy photons. Concomitant chemotherapy will consist of mitomycin C (10 mg/m², days 1 and 29) and 5-FU (1000 mg/m² for 4 daily continuous infusion, days 1–4 and 29–32).

Follow-up

After definitive CRT, patients will be re-evaluated by serial digital anorectal exploration and inguinal node palpation at 6-week intervals. HRA will be performed at 6, 12 and 24 weeks after CRT treatment. For assessment of lymph node involvement pelvic DW-MRI will be performed at 3 and 6 months after CRT treatment. Patients will undergo a local biopsy 6 months after end of treatment. Consideration of APR will be recommended in case of persistent disease. In case of complete clinical response, the patient will continue with a regular follow-up schedule, including (i) complete physical examination, HRA and endoanal ultrasound at 3-month intervals for an additional 2 years and every 6 months thereafter; (ii) annual chest/abdominal/pelvic CT and pelvic DW-MRI. Diagnostic exams will be anticipated in case of clinical suspicion of disease recurrence.

High-resolution anoscopy protocol and histopathologic examination

HRA acquisitions will be performed with a THD proctostation HRA. HRA data from all patients will be obtained at four measurement points: at diagnosis prior to CRT (HRA-I), 6 weeks after the end of CRT (HRA-II), 12 weeks after the end of CRT (HRA-III) and 24 weeks after the end of CRT (HRA-IV). For each patient, the procedure of HRA examination will be performed as follows: after wiping the anal canal mucosa with saline, the green filter will be used to evaluate vascular patterns at high magnification power. Then, 5% acetic acid will be used to the lesion to define the aceto-whitening score. Lastly, Lugol's solution will be applied to assess for the iodine intake score.

The biopsy specimen will be taken from the most suspicious area, with the patient under local anesthesia, at 6 months after end of treatment.

Statistical analysis and study end-point

Statistical analysis will be performed using the R 0.98.1091 software. Primary end-point is to detect the diagnostic accuracy of HRA in diagnosing persistent/recurrent disease in comparison to histopathologic examination (based on biopsy 6 months after CRT) and to define the appropriate scoring system for HRA after CRT. Sensitivity, specificity,

positive predictive value (PPV), negative predictive value (NPV) and accuracy of HRA scoring system will be calculated. Sensitivity will be defined as the number of patients with persistence at biopsy who were correctly identified (true positives) divided by the total number of patients with persistent disease (true positives + false negatives). Specificity will be defined as the number of patients with complete response at biopsy who were correctly identified (true negatives) divided by the total number of women receiving biopsy with complete response (true negatives + false positives). PPV will be calculated as the number of true positives divided by the total number of positive results (true positives + false positives). NPV will be defined as the number of true negatives divided by the total number of negative results (true negatives + false negatives). Accuracy will be calculated as the number of true positives plus true negatives (total number correct) divided by the total number of patients studied. We will assign a HRA score of 1 to each HRA parameter showing all the following performances: specificity $\geq 75\%$, PPV $\geq 50\%$, NPV $\geq 50\%$ and an accuracy of $> 60\%$.

In addition, standard descriptive statistics will be used to evaluate the distribution of each variable. Continuous variables will be reported as mean \pm standard deviation (SD) and categorical variables as frequencies or percentages. The chi-square test and Mann-Whitney U test will be used to compare groups for nominal and ordinal variables, respectively. Patients with a complete tumor regression within 3 months from the end of CRT will be classified as early responders, whereas patients who never attained local control within 6 months from the end of CRT will be classified as treatment failure. We will investigate the association between prognostic HRA pre- and post- treatment factors and the risk of treatment failure and recurrence. OS and distant metastasis-free survival (DMFS) will be calculated in months from the date of the end of CRT to the first event, including date of the last follow-up and death (OS) and/or first distant failure (DMFS). Local failure-free survival (LFFS) and locoregional failure-free survival (LRFFS) will be defined as the persistence, regrowth or recurrence in the primary tumor site (LFFS) or in regional lymph nodes (LRFFS) after definitive CRT. Both LFFS and LRFFS will be calculated in months and will be assessed 6 months after the end of initial treatment.

Based on the main COVID-19-related barriers in the process of conducting a reliable survival analysis – patients who will die due to COVID-19 respiratory disease should be (i) censored at the time of death because they are lost to follow-up (censored option); or (ii) included in the number of events (death) due to his/her advanced disease status (event option) [8] – the Covid-Death Mean-Imputation (CoDMI) algorithm will be used in survival analysis (A user-friendly version of CoDMI is available at <https://github.com/alef-innovation/codmi>) [9]. OS, LFFS, LRFFS, DMFS, and ADFS curves will be compared by the log-rank test. Numeric and categorical variables with a p -value < 0.05 will be included in a treatment failure risk score. Partial dependence plots will be generated to visualize the dependence between the outcome (treatment failure) and the single variables and, then, extrapolate those covariates that show better predictive ability. The non-parametric LOESS smoothing technique will be used to describe the relationship between continuous variables and outcome (treatment failure) in order to better define cut-off values to split variables into intervals [10]. Risk points of each subsequent variable interval and categorical variable will be obtained by fitting a logistic regression model [10]. Total score will be calculated to represent the prediction of the treatment failure event probability.

Estimated dates for completing accrual and presenting results

Expected complete 12 accrual in December 2023, with presentation of preliminary results by June 2024.

Discussion

Because of the similarity between anal canal and cervical mucosae,

we attempted to use gynecologic methods to examine the anal canal mucosa. Traditionally, assessment of colposcopy is based on the Reid's Colposcopic Index (RCI) [11]. RCI is a scoring system that takes into account (i) the degree of aceto-whitening; (ii) the characteristics of lesion margins; (iii) the vascular patterns; (iv) the degree of iodine uptake. As colposcopy per early cervical dysplastic lesion, HRA is a direct microscopic method and is the gold standard tool to detect early anal canal dysplastic lesions. HRA allows to map the full extent of the mucosa changes, visualize the vascular patterns of the anal canal mucosa and help direct biopsy placement. HRA scoring represents an ideal means of assessing response to CRT treatment and so far there is no accepted system for anal canal carcinoma. We attempted to quantify residual tumor and/or CRT-induced regressive changes and correlate them with patient outcome. The aim is to develop and validate a simple, prognostically significant and reproducible system for grading response of anal canal carcinoma to CRT on the basis of HRA examination that can be universally applied in routine HRA reporting.

To our knowledge, our analysis will be the first study that will investigate the potential combination of HRA application in anal canal cancer patients in a modern context, including 8th TNM staging system and IMRT technique. We will introduce for the first time a predictive modeling approach. The purpose of this study is to determine whether a HRA score can be created to predict the persistence/recurrence of anal cancer after definitive CRT using potential clinical predictors – such as human immunodeficiency virus (HIV) treatment history, smoking history, sexual history, human papillomavirus (HPV)-related lesions – and HRA features. A model for predicting which patients are at greatest risk for persistent/recurrent disease is needed in order to decrease the need for salvage demolitive surgery in this population. The model will allow clinicians to identify a population of patients who may benefit from further intensive treatment interventions.

In addition we will conduct a reliable survival analysis in order to provide a standard approach on how COVID19 deaths should be classified in survival analysis to obtain comparable results.

We hope to propose a predictive score that could help to guide future research in anal canal cancer field in COVID19 era.

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None.

CRedit authorship contribution statement

Francesca De Felice: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Ilaria Clementi:** Writing – review &

editing, Conceptualization, Methodology, Formal analysis, Data curation. **Valeria Converti:** Data curation. **Daniele Crocetti:** Data curation. **Paolo Sapienza:** Writing – review & editing. **Nadia Bulzonetti:** Data curation. **Sassun Richard:** Data curation. **Daniela Musio:** Writing – review & editing. **Andrea Mingoli:** Writing – review & editing. **Vincenzo Tombolini:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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