Stability of metabolic tumor volume may enable radiotherapy dose painting in anal cancer

Ana María Acosta Roa a,*, Vilde Eide Skingen b, Bernt Louni Rekstad a, Christine Undseth c, Espen Rusten a, Eivør Hernes d, Marianne Grønlie Guren e, Eirik Malinen a, f

a Department of Medical Physics, Oslo University Hospital, Oslo, Norway
b Department of Radiation Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway
c Department of Oncology, Oslo University Hospital, Oslo, Norway
d Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway
e Institute of Clinical Medicine, University of Oslo, Oslo, Norway
f Department of Physics, University of Oslo, Oslo, Norway

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ABSTRACT

Purpose: To evaluate the variability of the 18F-FDG-PET/CT-based metabolic tumor volume (MTV) in anal cancers during fractionated chemoradiotherapy (CRT), and assess the impact of this variability on dosimetric accuracy in MTV-targeted dose painting.

Methods: Eleven patients with anal squamous cell carcinoma who received fractionated chemoradiotherapy with curative intent were included. 18F-FDG PET/CT images were acquired at pre- and mid-treatment. Target volumes and organs at risk (OARs) were contoured manually on both image series. The MTV was generated from the PET images by thresholding. Treatment plans were retrospectively optimized for both image series using volumetric modulated arc therapy (VMAT). Standard plans prescribed 48.6 Gy, 54 Gy and 57.5 Gy in 27 fractions to elective regions, lymph node metastases and primary tumor, respectively. Dose painting plans included an extra dose level of 65 Gy to the MTV. Pre-treatment plans were transferred and re-calculated at mid-treatment basis.

Results: MTV decreased from pre- to mid-treatment in 10 of the 11 patients. On average, 71 % of MTV overlapped with MTV. The median and mean doses to the MTV were robust against anatomical changes, but the transferred dose painting plans had lower D98% values than the original and re-optimized plans. No major differences were found between standard and dose painting plans for OARs.

Conclusions: Despite volumetric changes in the MTV, adequate dose coverage was observed in most dose painting plans. The findings indicate little or no need for adaptive dose painting at mid-treatment. Dose painting appears to be a safe treatment alternative with similar dose sparing of OARs.

1. Introduction

Anal cancer is a relatively rare disease but has shown considerable increased incidence over the past three decades [1,2]. Standard radical treatment of loco-regional anal cancer is chemoradiotherapy (CRT), where intensity-modulated radiotherapy (IMRT) or similar is the recommended radiation delivery approach [3]. Residual or recurrent disease is observed in 15–25 % of cases, with the majority of relapses occurring within 2 years after treatment [4]. Moreover, a common site of relapse is at the location of the primary tumor [5]. This indicates that new approaches to improve anal cancer outcomes should focus on local treatment intensification in selected high-risk patients.

Positron emission tomography (PET) is a well-established technique for cancer detection [6]. Anal cancers are typically hypermetabolic and show high uptake of 18F-fluorodeoxyglucose (18F-FDG) in PET. In addition, the metabolic tumor volume (MTV) has shown an independent predictive role for CRT outcomes in terms of loco-regional control in anal cancer [7–9]. Furthermore, sustained high 18F-FDG-uptake during and after treatment may reveal clonogenic cell survival and proliferation, thus indicating treatment failure [7,10]. Therefore, 18F-FDG-PET during the course of treatment can potentially be used to assess treatment response and need for adaptation of treatment.

* Corresponding author at: Department of Medical Physics, Oslo University Hospital, P.O. Box 4953 Nydalen, N-0424 Oslo, Norway.
E-mail address: anaaco@ous-hf.no (A.M. Acosta Roa).

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Dose painting is a technique to escalate the dose to specific parts of the tumor, thus increasing control over radiosensitive tumor areas. Dose painting by contours follows the same optimization principles as in a simultaneous integrated boost (SIB), where the region to be boosted is a subvolume of the tumor. In 18F-FDG-PET guided dose painting of anal cancer, the MTV is a logical boost region due to its association with locoregional failure. Still, significant interfractional motion and alterations in the tumor volume during fractionated radiotherapy may have dosimetric consequences that may reduce the clinical effect of the boost. On the other hand, one may consider adapting the treatment according to changes in the MTV. To our knowledge, the volumetric stability of the MTV in radiotherapy of anal cancer in general, and in dose painting in particular, has not been previously investigated.

In the current work, we employ 18F-FDG-PET/CT images of patients with anal cancer prior to and approximately two weeks into the course of standard CRT with the aim to assess the variability in MTV and the subsequent dosimetric impact in dose painting. The PET/CT image series were used retrospectively to simulate dose painting, both in an adaptive and non-adaptive setting. MTVs were generated for both imaging sessions and used as the dose painting boost volume. We studied the overlap between MTVs obtained at pre- and mid-treatment to connect volumetric with dosimetric consequences. The work will thus shed light on the potential clinical applicability of MTV-based dose painting in anal cancer.

2. Materials and methods

2.1. Patient population

This retrospective study was conducted on patients enrolled in the prospective study Anal Cancer Radiotherapy (ANCARAD) at Oslo University Hospital, NCT01937780 [4]. Patients were eligible for inclusion if they had histologically proven squamous cell carcinoma of the anal canal and were scheduled for CRT. Signed informed consent was obtained from all patients, and the regional ethical committee approved the study. A subset of 39 patients were asked and consented to an extra PET/CT 2 weeks into CRT. The selection was partly based on logistics such as the capacity and availability of PET/CT in the current week. Of these, 11 patients with representative characteristics (stage and MTV prior to treatment) were selected for this study. CRT was delivered according to national guidelines [11] based on international recommendations [13]. The gross tumor volume (GTV) included the anal circumferential area of the tumor and, in some cases, certain perianal and/or rectal regions, based on diagnostic imaging (MRI and PET) and clinical examination. The GTV was expanded by 1.5 cm and manually adjusted to include the whole anal canal, from the anal verge to the ano-rectal transition, as well as the internal and external sphincter to form a clinical target volume (CTV). Positive lymph nodes were delineated (GTV) and expanded by 0.7 – 1.0 cm to form CTV. The following regions were included in the elective CTV (CTV): mesorectum, presacral space, ischiorectal fossa, internal iliac nodes, obturator nodes, inguinal nodes and for high risk patients, also the external iliac nodes. Ventrally the CTV included 0.5 – 1.0 cm into movable structures. Planning target volumes (PTVs) were defined as an expansion of the CTVs with 0.8 cm, but 1.1 cm in the ventral direction. A smaller margin of 0.5 – 1.0 cm was used isotropically for positive lymph nodes. Due to anatomical differences from pre- to mid-treatment, the CTVs were recontoured by an oncologist on the mid-treatment PET/CT images.

The MTV was generated from PET images by adaptive thresholding. This was performed in the contouring module of the treatment planning system (Eclipse, Varian). The threshold activity ($A_{\text{threshold}}$ [Bq/ml]) was found from the maximum intensity ($A_{\text{maximum}}$) and the background activity ($A_{\text{background}}$) measured in gluteal muscles [14] as the mean of the activity over at least 6 randomly selected pixel values, according to

$$A_{\text{threshold}} = A_{\text{background}} + c_1 \cdot (A_{\text{maximum}} - A_{\text{background}})$$

where $c_1$ is a threshold constant of value 0.2 and 0.3 for the pre- and mid-treatment PET images, respectively. The change in threshold constant was necessitated by the decrease in tumor activity at mid-treatment compared to pre-treatment. From this, the MTV at pre-treatment (MTV$_{\text{pre}}$) and the MTV at mid-treatment (MTV$_{\text{mid}}$) were generated, as shown in Fig. 1. No margin was applied to MTV, as this volume resides within PTV, and thus receives at least the prescribed conventional tumor dose.

Organs at risk were contoured by a radiotherapy technician and approved by an oncologist. Intestinal cavity was delineated from 1 to 1.5 cm cranial from the border of PTV of the elective lymph nodes (PTV$_{\text{L}}$) down to the most inferior bowel loop or the recto-sigmoid junction, excluding muscles, vessels and other organs than bowel [15,16]. The circumference of the bladder was contoured. Femoral heads were contoured, excluding the femoral neck.

2.2. Imaging protocols

Medical imaging was conducted according to the existing clinical protocols. Pre-treatment imaging for staging and treatment planning comprised T2-weighted and diffusion weighted Magnetic Resonance Imaging (MRI), 18F-FDG-PET/CT, and a contrast-enhanced CT. Additionally, a mid-treatment study-specific pelvic 18F-FDG-PET/CT was acquired around the tenth radiotherapy fraction. PET scans were acquired using a Biograph mCT 40 (Siemens Medical Solutions, Erlangen, Germany) after at least 6 h of fasting and 1 h after injection of approximately 255 MBq (3 MBq/kg) of 18F-FDG. Images were reconstructed using the OSEM 2i21 algorithm, with a three-dimensional point spread function (3D PSF), correction for time of flight (TOF) and 2 mm Gaussian filter. A $400 \times 400$ reconstruction matrix was used with $2 \times 2$ mm in-plane resolution and $3$ mm slice thickness. A standard attenuation correction algorithm was applied on the non-contrast enhanced low-dose CT. Glucose level was acceptable and below 7 mmol/L for all patients. Planning CT scans were performed on a LightSpeed Pro 16 (GE Healthcare, Chicago, Illinois, USA) using 135 ml Iomeron as contrast agent. The axial resolution was $< 1$ mm and the slice spacing was 2.5 mm. Images were rigidly co-registered using the built-in algorithm of the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA).

2.3. Contouring

Target volume delineation and application of margins were done according to national guidelines [11] based on international recommendations [13]. The gross tumor volume (GTV$_{\text{v}}$) included the anal circumferential area of the tumor and, in some cases, certain perianal and/or rectal regions, based on diagnostic imaging (MRI and PET) and clinical examination. The GTV$_{\text{v}}$ was expanded by 1.5 cm and manually adjusted to include the whole anal canal, from the anal verge to the ano-rectal transition, as well as the internal and external sphincter to form a clinical target volume (CTV). Positive lymph nodes were delineated (GTV$_{\text{v}}$) and expanded by 0.7 – 1.0 cm to form CTV. The following regions were included in the elective CTV (CTV): mesorectum, presacral space, ischiorectal fossa, internal iliac nodes, obturator nodes, inguinal nodes and for high risk patients, also the external iliac nodes. Ventrally the CTV included 0.5 – 1.0 cm into movable structures. Planning target volumes (PTVs) were defined as an expansion of the CTVs with 0.8 cm, but 1.1 cm in the ventral direction. A smaller margin of 0.5 – 1.0 cm was used isotropically for positive lymph nodes. Due to anatomical differences from pre- to mid-treatment, the CTVs were recontoured by an oncologist on the mid-treatment PET/CT images.

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2.4. Overlap between pre- and mid-therapy MTV

In order to measure the volume of the union and overlap between the MTV$_{\text{pre}}$ and MTV$_{\text{mid}}$ volumes, contoured on the pre- and mid-treatment PET/CT series, respectively, these volumes were copied to the contrast

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**Table 1**

Patient demographics and tumor characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female/Male</td>
</tr>
<tr>
<td>Age, years</td>
<td>8/3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>62 (40–73)</td>
</tr>
<tr>
<td>Tumor stage*</td>
<td>T2/T3</td>
</tr>
<tr>
<td></td>
<td>8/3</td>
</tr>
<tr>
<td>Nodal stage*</td>
<td>N0/N1/N2/N3</td>
</tr>
<tr>
<td></td>
<td>4/1/5/1</td>
</tr>
</tbody>
</table>

*aAccording to TNM classification, 7th edition [12].
3. Results

Fig. 2 shows an example of treatment plan generation for a study patient prior to RT. Comparing standard radiotherapy (RT) and dose painting (Fig. 2C vs 2D), we see negligible differences in the dose distribution outside the GTV. Pre- and mid-therapy MTVs, as well as overlap volumes, are shown in Table 3. The MTV observed at mid-therapy PET/CT was smaller than that at baseline in 10 of the 11 patients, while there were no volumetric changes in one patient. The median of the pre- and mid-therapy MTV were 6.2 and 1.9 cm$^3$, respectively ($p = 0.005$), indicating a 71% reduction after 10 fractions of RT. The median overlap volume between MTV$_{pre}$ and MTV$_{mid}$ was 1.6 cm$^3$, with a corresponding median OF of 0.71, indicating a substantial overlap.

Dose statistics for MTV for original, transferred and re-optimized (adapted) plans for standard and dose painting regimes are shown in Fig. 3. A dosimetric comparison of changes from pre- to mid-therapy for the MTV is provided in the Supplemental Material. The median (D$_{95\%}$) and mean doses (D$_{mean}$) to the MTV were robust against anatomical variations from pre- to mid-treatment for both the standard and dose

### Table 2

<table>
<thead>
<tr>
<th>Volume</th>
<th>Recommended Dose</th>
<th>Required Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV$_n$</td>
<td>D$_{95%}$ ≥ 56.4 Gy</td>
<td></td>
</tr>
<tr>
<td>GTV$_e$</td>
<td>D$_{95%}$ ≥ 52.9 Gy</td>
<td></td>
</tr>
<tr>
<td>PTV$_e$</td>
<td>D$_{95%}$ ≥ 61.5 Gy</td>
<td>D$_{mean}$ ≥ 54.6 Gy</td>
</tr>
<tr>
<td>PTV$_n$</td>
<td>D$_{95%}$ ≤ 57.8 Gy</td>
<td>D$_{mean}$ ≥ 51.3 Gy</td>
</tr>
<tr>
<td>PTV$_e$</td>
<td>D$_{mean}$ ≥ 46.2 Gy</td>
<td>D$_{mean}$ ≥ 68.2 Gy</td>
</tr>
<tr>
<td>MTV$^*$</td>
<td>D$_{mean}$ ≥ 61.7 Gy</td>
<td></td>
</tr>
<tr>
<td>Intestinal Cavity</td>
<td>V$_{150Gy}$ &lt; 195 cm$^3$</td>
<td></td>
</tr>
<tr>
<td>Femoral Head</td>
<td>D$_{max}$ &lt; 52.5 Gy</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>D$_{mean}$ &lt; 45 Gy</td>
<td></td>
</tr>
<tr>
<td>Pubic Bone</td>
<td>D$_{mean}$ &lt; 52.5 Gy</td>
<td></td>
</tr>
</tbody>
</table>

$^*$ Only used for optimization of the dose painting treatment plans (not included in the NOAC8 protocol [18]).
The delineated MTV is shown by the red contour, PTVs for tumor PTV in either of the treatment regimes. The mean dose to the bladder, the V\textsubscript{45Gy} to the intestinal cavity and the D\textsubscript{2\%} to the femoral heads, individually, were analyzed for all painting plans. Median doses for transferred plans were 57.9 ± 0.7 Gy and 65.5 ± 2.0 Gy for the standard and escalated dose regimes, respectively. Likewise, mean dose to the MTV in transferred plans was 57.9 ± 0.7 Gy and 65.1 ± 1.9 Gy, respectively. No significant difference was found between the original and transferred treatment plans for neither standard nor dose painting regimes. Differences in dose coverage to 98 % of the MTV between transferred and original standard treatment plans were not significant (57.1 ± 0.7 Gy and 57.1 ± 0.8 Gy for original and transferred plans, respectively). However, transferred dose painting plans had lower D\textsubscript{90\%} values compared to original plans (63.8 ± 0.7 Gy and 61.9 ± 3.3 Gy, respectively; p = 0.047). Still, the transferred dose painting plans maintained a much higher dose level in the MTV compared to the standard plans. Re-optimized plans at mid-therapy gave highly similar dose statistics as the pre-therapy plans for MTV. Transfer of original dose plans to mid-therapy basis did not result in major changes in the maximum dose (D\textsubscript{max}), as median D\textsubscript{max} doses changed from 59.2 ± 0.5 Gy to 59.0 ± 0.9 Gy in the standard plans and from 67.1 ± 0.8 Gy to 66.7 ± 0.9 Gy in the dose painting plans. Differences in D\textsubscript{max} to the MTV between original and transferred plans were not significant in either of the treatment regimes.

The mean dose to the bladder, the V\textsubscript{45Gy} to the intestinal cavity and the D\textsubscript{2\%} to the femoral heads, individually, were analyzed for all treatment plans in both branches of the study. Dose statistics for the selected OARs are shown in Fig. 4. No significant differences were found between standard and dose painting plans for the studied OAR dose parameters, with the exception of V\textsubscript{45Gy} to the intestinal cavity in which dose painting gave a slightly lower population mean (p = 0.042; Supplemental Material).

4. Discussion

In the present study, we have used 18F-FDG-PET/CT of anal cancer to define the MTV as a boost volume and to retrospectively create treatment plans for a standard and an escalated dose painting radiotherapy regime at both pre- and mid-treatment anatomy. We have studied the dosimetric impact of changes in the MTV and relevant organs at risk for both standard treatment plans and for PET-based dose painting plans in the mid-treatment images. The main findings were that although the MTV showed noticeable changes in terms of shrinkage during the first 10 fractions, the dosimetric consequences with respect to boost dose coverage at mid-treatment were not very pronounced.

Approximately 75 % of relapses in anal cancer occur on the original tumor site [19,20]. Several studies have reported two-year survival after CRT of anal cancer patients, from which a tumor control probability model has been developed by Muirhead et al. [21]. Their model shows a potential benefit of dose escalation on tumor control. In the current study, under the assumption that metabolically active cells, defined by 18F-FDG-PET, are the optimal targets for the radiotherapy boost, the dose boosting of these cells may have a positive effect on tumor control. This requires that the MTV is included in the boost volume throughout the fractionated treatment, as was largely demonstrated herein.

Because of the high metabolic activity of anal carcinomas [22], 18F-FDG-PET/CT will in most cases facilitate a straightforward delineation of the MTV. The spatial stability of 18F-FDG-avid subvolumes of the GTV from pre-treatment to fraction 8 or 9 was previously studied and evaluated in a population of 20 anal cancer patients [23]. The OF between the 18F-FDG-PET subvolumes defined at pre- and mid-therapy was on average better than 0.8, but was dependent on thresholding procedure. That finding is comparable to the OF in our study of 0.71, and Sabbagh
et al. concluded in [23] that the 18F-FDG-PET subvolume is consistent throughout a CRT treatment course. This is further supported by observations that anal tumors show little motion during fractionated radiotherapy, with an interfraction variability in the order of 1–3 mm, as evident from repeat cone beam CT [24].

For delineation of the MTV, we used a semi-automatic technique (adaptive thresholding) based on activity values for maximum and background intensities. This method may perform well in situations where the background and tumor uptake levels vary through the course of fractionated radiotherapy. The activity in the gluteal muscles was chosen as the reference background. It has been found that activity uptake in muscle is more stable than in liver, and should therefore be preferred as background in 18F-FDG PET/CT [14]. We have previously found that pelvic irradiation will cause a decrease in the tumor uptake for these patients [7]. Thus, a standard thresholding procedure using e.g. 50 % of the maximum tumor activity level at mid therapy will greatly overestimate the MTV [23], as a greater share of background tissue will be included. In our adaptive thresholding, a c value of 0.2 and 0.3 had to be used at pre- and mid treatment to appropriately delineate the hypometabolic part of the tumor, indicating the challenge with standardizing MTV segmentation for different tumor/background situations. Previous studies of 18F-FDG uptake in lung [25] and pancreatic tumors [26] advise the use of a threshold yielding an OF of 0.7 or higher as a good delimitier for a biological boost, supporting the current MTV segmentation.

We included 11 patients in the current study, as re-contouring and planning also in the mid-therapy PET/CT basis is very time consuming. In the Supplemental Material, the MTV pre of a group of 39 patients included in the ANCARAD study [4] and studied in [7] is compared to the group of 11 patients included in this study. The segmentation method in [7] is based in 50 % of SUVpeak and does not correct for background activity. However, the MTV pre volumes in that study and the current are comparable because the background correction will only be significant at mid-treatment when the signal-to-noise ratio is lower. The MTV pre volumes in the two groups show similar characteristics (p = 0.8), which gives a strong indication of a representative patient population in this study. A disadvantage of this study is that, because we created the treatment plans retrospectively, it is impossible to assess how much the MTV would change from pre- to mid-treatment during an actual dose painting treatment regime. However, at 10 fractions, the additional dose given to MTV following our proposed dose painting protocol is only 2.8 Gy higher than what was actually given to the patients at the time of mid-therapy imaging (21.3 Gy). This 13 % increase in dose would give a slightly smaller MTV, but this will only give minor changes in the treatment plans and not affect e.g. OAR doses. It is however possible that greater changes in the MTV occur at later time points in the fractionated schedule.

In this work, recommended dose limits to the OARs from the NOAC8 protocol [18] were used as guidelines for the treatment plans. We observed that these limits were in general feasible for the optimizer, regardless of dose regime. Nevertheless, mean dose to the bladder and V45Gy to the intestinal cavity were in some cases above the recommendations. It is, however, important to point out that the recommended dose limits in [18] for the intestinal cavity and the bladder are given as second and fourth priorities, respectively, under the dose coverage to targets, stated as first priority. However, if MTV was too close to an OAR,
the coverage to the MTV in the dose painting treatment plans could be compromised. Current National guidelines [11] have updated the recommendations for doses to the intestinal cavity, \( V_{30Gy} < 310 \text{ cm}^3 \), and \( V_{40Gy} < 70 \text{ cm}^3 \), with grade 3 diarrhea as endpoint. Nevertheless, these guidelines specify that because of the difficulty to fulfill these requirements, the lowest achievable dose to the intestinal cavity with acceptable dose to PTV should be aimed for. There is however, some disagreement in the literature regarding suggested dose limits to the intestinal cavity. In [27] \( V_{45Gy} < 150 \text{ cm}^3 \) is suggested (concomitant cisplatin in half of the sample patients), with grade 2 toxicity RTOG as endpoint, whereas in [28] \( V_{45Gy} < 250 \text{ cm}^3 \) to the whole intestinal cavity is suggested as a limit for the same endpoint. It is important to stress that \( V_{45Gy} \) to intestinal cavity and \( D_{\text{mean}} \) to the bladder were not higher for the dose painting treatment plans in this study. The reason may be that both the intestinal cavity and the bladder are adjacent to the PTV, PTV_0, and PTV_1, for which the prescribed dose is the same in both treatment regimes. The MTV is surrounded by the PTV, thereby providing the optimizer a margin for a steep dose fall-off in the dose painting plans. The same rationale applies for the rest of the analyzed OARs (at greater distances from the MTV), for which dose levels were also similar in both standard and dose painting plans.

5. Conclusions

Despite volumetric changes in the MTV, adequate dose coverage was observed in the dose painting plans apart from underdosage of a small part of the volume. The lowest dose level in these parts of the MTV in the dose painting plans is however higher than the dose prescribed in the standard treatment approach. The findings indicate little or no need for adapted dose painting. Dose painting appears to be a safe treatment alternative with similar dose sparing of OARs compared to a standard regime.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2023.103151.

References