Physics and Imaging in Radiation Oncology 25 (2023) 100424

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Original Research Article

# Estimated dose to site of loco-regional recurrence after radiotherapy in anal cancer using point of origin methods

Karen Lycke Wind [a,b,*], Karen-Lise Garm Spindler [a,b], Christina Maria Lutz [c], Lars Nyvang [c], Camilla Kronborg [b,d]

[a] Department of Experimental Clinical Oncology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
[b] Department of Clinical Medicine, Faculty of Health, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
[c] Department of Oncology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
[d] Danish Centre for Particle Therapy, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark

ARTICLE INFO

*Keywords:*
Pattern of failure
Loco-regional recurrence
Anal cancer
Point of origin
Deformable image registration

ABSTRACT

*Background and purpose:* Loco-regional recurrence (LRR) dominates the failure pattern after curative radiotherapy in anal cancer. The aim of this study was to estimate dose of LRRs in anal cancer using a point of origin-based method.

*Method and materials:* Of 321 patients with squamous cell carcinoma of the anus, 31 patients with LRR (29 local recurrences and 5 regional lymph node recurrences) were available for analysis. The recurrence volumes were delineated on recurrence magnetic resonance imaging (rMRI). Rigid and subsequent deformable co-registration of planning computerised tomography scans and rMRI were performed. Point of origin was estimated as the centre of mass (COM) and an observer-based point of origin (obs-PO). Doses to COM and obs-PO, as well as the full recurrence volume, were estimated and the relation to target volumes was extracted.

*Results:* The median minimum dose to COM was 63.8 Gy (range 32.5–65.1 Gy) and 63.7 Gy (range 35.5–65.2 Gy) to obs-PO of local recurrences. COM was included in the high dose volume (64 Gy) in 86 % of cases, and obs-PO was included in 75 % of cases. There was no difference in minimum dose to COM and obs-PO, and the median distance between the two points was 3.3 mm (range 0.6–19.8 mm). No recurrences occurred in primarily boosted lymph nodes.

*Conclusion:* The majority of LLRs were located within the high dose volume indicating radioresistance as the primary cause of recurrence in anal cancer. No difference between the use of COM and obs-PO was evident.

## 1. Introduction

Modern radiotherapy (RT) techniques such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) are standard of care in the treatment of anal cancer [1–3]. Anal cancer is considered a loco-regional disease, and failure within the pelvic area is seen in approximately 20–30 % of patients [4–6]. Hence, to improve the outcome of anal cancer, improved local control is necessary.

Loco-regional recurrence (LRR) can be caused either by surviving radioresistant cancer stem cells despite potentially curative doses or geographical miss of the tumour and thereby insufficient radiotherapy dose [7]. Assuming isotropic growth of a recurrence, the point of origin can be estimated as the centre of mass (COM) of the recurrence volume [8,9]. However, the shape of especially large recurrences is often irregular, and the isotropic growth pattern model can be compromised due to anatomical barriers such as pelvic bone, muscles of the pelvic wall or other nearby organs. In these cases, an observer-based point of origin (obs-PO) may be a better estimate of the origin of the recurrence [10,11].

In previously published studies of anal cancer recurrences, only total recurrence volume in relation to different dose volumes has been used to estimate whether the recurrence was in-field, marginal, or out-of-field and/or a simple estimation of relation to standard irradiated areas [12–17]. This "volumetric approach" is, however, highly dependent on the size of the recurrence at the time of diagnosis and is, therefore, time-dependent [10]. No previous studies have measured the dose to anal cancer recurrences based on the original radiotherapy plan. With the

* Corresponding author.
*E-mail address:* karen.lycke.wind@auh.rm.dk (K. Lycke Wind).

https://doi.org/10.1016/j.phro.2023.100424
Received 17 October 2022; Received in revised form 31 January 2023; Accepted 31 January 2023
Available online 3 February 2023

introduction of more conformal RT techniques evaluation of the dose to recurrence point of origin is highly relevant for dose planning optimisation.

This study aimed to estimate the dose to recurrence point of origin and full recurrence volume using a computerised workflow. In addition to this, the LRR pattern was analysed in terms of recurrence volume and pelvic location.

## 2. Materials and methods

### 2.1. Patient selection

In total, 321 patients with squamous cell carcinoma of the anus treated with definitive IMRT/VMAT at Aarhus University Hospital from 2007 to 2018 were identified and reviewed. Patients were identified using the International Statistical Classification of Diseases and Related Health Problems (ICD) diagnosis codes. Information on pre-treatment characteristics, treatment, and outcome was retrospectively retrieved from medical records. Patients were reclassified by the 8th edition of the TNM classification system [18]. By review of patient records, patients with LRR were identified. Only patients with an LRR, defined as relapse after a registered clinical and/or pathological complete response, were candidates for analysis, thus excluding patients with persistent disease at response evaluation. Recurrences were classified as local (LR) if the recurrence originated from the anal canal/rectum in the pelvis or regional (RR) if the recurrence was located in regional lymph nodes, including inguinal lymph nodes. The location of recurrences was classified by intrapelvic compartments (infralevator, central, posterior or anterior below peritoneal reflection) as by the PelvEx Collaborative guideline [19]. In total, 34 patients with LRR were identified, and of these, 31 had a diagnostic rMRI scan and were available for further analysis (Fig. 1). Information on gender, age, tumour stage and treatment characteristics are available in Table 1. Data collection was approved by the Danish Patient Safety Authority (3–3013-2447/1) and the Danish Data Protection Agency (1–16-02–66-18). Informed consent was waived with approval from the Danish Patient Safety Authority.

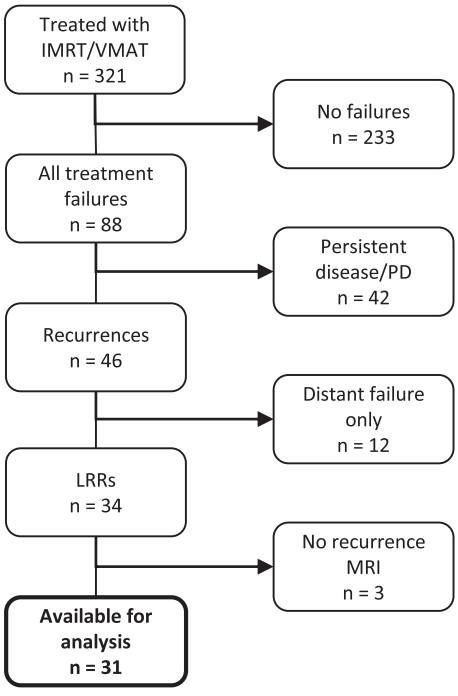


**Fig. 1.** Flowchart of patients available for analysis. Abbreviations: IMRT = Intensity-modulated radiation therapy, VMAT = volumetric modulated arc therapy, PD = progression disease, LRR = loco-regional recurrence, MRI = magnetic resonance imaging.

**Table 1**
Pre-treatment and treatment characteristics of the 31 patients included in the study.

| Pre-treatment characteristics | n = 31 |
|---|---|
| **Age at diagnosis (years), median (range)** | 57 (41–76) |
| **Gender** | |
| Male | 8 (26 %) |
| Female | 23 (74 %) |
| **Performance status (PS)** | |
| PS0 | 20 (65 %) |
| PS1 | 3 (10 %) |
| NA | 8 (26 %) |
| **Smoking status** | |
| Never smoker | 13 (42 %) |
| Former smoker | 5 (16 %) |
| Smoker | 12 (39 %) |
| NA | 1 (3 %) |
| **Maximum tumour size (cm), median (range)** | 4 (1–9) |
| ***T*-stage** | |
| T1 | 5 (16 %) |
| T2 | 19 (61 %) |
| T3 | 7 (23 %) |
| ***N*-stage** | |
| N0 | 22 (71 %) |
| N1a | 9 (29 %) |
| **Stage (8th edition)** | |
| Stage I | 5 (16 %) |
| Stage IIA | 16 (52 %) |
| Stage IIB | 1 (3 %) |
| Stage IIIA | 3 (10 %) |
| Stage IIIC | 6 (19 %) |
| **p16 status** | |
| Positive | 13 (42 %) |
| Negative | 1 (3 %) |
| NA | 17 (55 %) |
| **Treatment characteristics** | |
| **Radiotherapy** | |
| Radiotherapy | 18 (58 %) |
| Radiotherapy + chemotherapy (concomitant or induction) | 13 (42 %) |
| **Radiotherapy technique** | |
| IMRT | 10 (32 %) |
| VMAT | 21 (68 %) |
| **Prescribed dose** | |
| 64GY/51.2GY/32F | 30 (97 %) |
| 64GY/32F | 1 (3 %) |
| **Overall RT treatment time (days), median (range)** | 46 (43–51) |

Abbreviations: n = numbers, IMRT = intensity-modulated radiotherapy, VMAT = volumetric modulated arc therapy, GY = Gray, F = fractions, RT = radiotherapy.

### 2.2. Treatment planning

All patients had a planning computed tomography (pCT) scan with intravenous contrast and 3 mm slice thickness performed in supine position according to local protocol with flexed hip and knees. In 2011/2012, planning magnetic resonance imaging (pMRI) and positron emission tomography (pPET) scans were introduced as a supplement to pCT scans for target definition. Target definition (tumour (GTV-T) and pathological lymph nodes (GTV-N)) was based on planning and diagnostic imaging together with information from clinical staging and pathology reports. Target definition guidelines changed during the study period, but in general, a margin of 5–10 mm was added to the GTV-T to create the clinical target volume (CTV), followed by an additional 5 mm margin to account for internal movement creating the internal target volume (ITV). Individual modification in ITV margin was allowed to account for bowel and bladder movement. Both CTV and ITV were adjusted not to include bone and pelvic muscles. Standard elective lymph node volumes included the mesorectal, pre-sacral, ischioanal, inguinal, and internal- and external iliac lymph nodes, but individual

modifications were allowed. A planning target volume (PTV) margin of 5 mm anterior-posterior and lateral, and 8 mm craniocaudally was added to ITV. Standard dose to ITV (tumour and pathological lymph nodes) was 64 Gy delivered in 32 fractions (ITV64), and 51.2 Gy to the elective lymph node volume (ITV51.2). ITV and PTV were covered to 95–107 % of prescribed dose. Treatment planning was performed in Eclipse (Varian Medical Systems, CA, USA), and for dose calculation, a pencil beam algorithm (2007–2009) and the anisotropic analytical algorithm, AAA, (2009–2018) were used. Dose differences resulting from this were ignored as the difference in the pelvic area is minimal [20]. The earliest patients were treated with six field IMRT, while patients from 2011 primarily received VMAT. All patients were treated with daily imaging setup, which changed from orthogonal kV images (2007–2010) to cone-beam CT (2010–2018). For all patients, registration of the pelvic bones was used for setup. All patients received the planned fractions; however, two patients had an unplanned treatment break longer than one day.

### 2.3. Dose estimation

pCT and recurrence MRI (rMRI) were transferred to the Medical Image Merge (MIM) software (Cleveland, USA, version 7.2.1). The recurrence volume ($V_{rec}$) was delineated on the rMRI (axial T2 weighted sequences) aided by the radiologist report, clinical information and/or the pathology report from salvage surgery. In case of simultaneous local- and regional lymph node recurrence, all failure sites were delineated separately. For all LRs, an obs-PO was marked based on where the recurrence on the rMRI appeared to originate, e.g. if an obvious tumour centre in the bowel lumen were present. In case of two separate LR, only one obs-PO was estimated. For the limited volumes of regional lymph node recurrences, COM or total lymph node volume were considered adequate for dose estimation and obs-PO were therefore not delineated. Two oncologists (including one radiation specialist) performed the recurrence delineation and estimation of obs-PO.

Co-registration of pCT and rMRI scans and dose estimation was performed in the MIM software. The first step of the workflow was an automated rigid registration using six degrees of freedom with both translation along and rotation around the x-, y- and z-axis. If relevant, a manual correction was performed with focus on the inner line of the pelvic bones (sacral and iliac bone) and the soft tissue in relation to the recurrence. Based on this, an automated multimodality deformable registration (DIR) of the pCT and rMRI was performed [21].

The $V_{rec}$ and the obs-PO structures were deformable transferred from the rMRI to the pCT scan. The results were visually inspected, and if anatomical changes were not accounted for satisfactorily, for example bowel lumen differences, the obs-PO could be manually adjusted. The COM of the transferred recurrence structure was then calculated by the MIM workflow. For dose estimation, a sphere of 2.5 mm was added to the centre of both the obs-PO and COM. Minimum, mean and maximum dose to the obs-PO, COM and $V_{rec}$ were measured, and the overlap with GTV and ITV volumes was determined by the number of voxels of the different contours ($V_{rec}$, COM and obs-PO) overlapping with the voxels of the target volumes relative to the total voxel count of the different contours.

### 2.4. Statistics

Descriptive statistics (numbers, percentage and median) were used to present pre-treatment, treatment, and recurrence characteristics. The median minimum, mean and maximum dose between COM and obs-PO was compared using Wilcoxon signed-rank test for paired non-parametric data. A p-value $\leq 0.05$ was considered significant. Overall survival at three and five years was calculated using the Kaplan-Meier method and was calculated from the date of diagnosis to the date of death. Median time to recurrence was calculated from the date of last delivered fraction to the date of recurrence.

## 3. Results

Of the 31 patients with available rMRI, 29 had LR, with one patient having two separate tumours (the smaller of the two tumours was considered a local bowel metastasis). Three patients had both local- and regional lymph node recurrence, and two patients had regional lymph node recurrence only. Regional lymph node recurrences were located in mesorectal (n = 2), inguinal (n = 2) and internal iliac (n = 1) lymph nodes. Of the 31 patients, three patients had synchronous distant recurrence located in the liver (n = 2) and para-aortic lymph node (n = 1). Recurrence characteristics, including location and median volume, are available in Table 2. The median time from the last day of RT to recurrence diagnosis was 21.5 months (range 4.7–85.8 months), and overall survival at 3- and 5 years were 84 % and 63 %, respectively.

### 3.1. Dose estimation

Table 3 shows minimum, mean and maximum dose (median) to COM, obs-PO and $V_{rec}$ for LRs. The prescribed minimum dose (median) of LRs was 62.8 Gy (range 0–64.1 Gy) for $V_{rec}$, 63.8 Gy (range 32.5–65.1 Gy) for COM and 63.7 Gy (range 35.8–65.2 Gy) for obs-PO. There was no statistically significant difference between median minimum dose to COM and obs-PO ($p = 0.4$). Minimum dose to all individual recurrences (LR and regional lymph node recurrence) is depicted in Fig. 2, showing the minimum dose to $V_{rec}$, COM and obs-PO. For LRs, 90 % of both COM and obs-PO received 95 % of prescribed dose to ITV64, and 76 % of $V_{rec}$ received 95 % of prescribed dose to ITV64.

For LRs, COM was 100 % included in ITV64 in 86 % of cases, obs-PO in 75 % of cases and $V_{rec}$ in 45 % of the cases, whereas 97 % of all volumes were included in the ITV51.2 volume. Location in relation to GTV-, ITV64- and ITV51.2 volumes for COM (LR and regional lymph node recurrences) is simplified in Fig. 3. A more detailed figure of COM, obs-PO and $V_{rec}$ and relation to target volumes are available in Supplementary Fig. S1. Median centroid distance from obs-PO to COM was 3.3 mm (range 0.6–19.8 mm).

None of the recurrent regional lymph nodes was boosted at primary treatment. Doses to COM and $V_{rec}$ depended on inclusion of elective volume and can be seen in Supplementary Table S1.

Manual corrections of the rigid registration were necessary for

**Table 2**
Loco-regional recurrence characteristics and recurrence treatment.

| **Loco-regional recurrence** | **n = 31** |
|---|---|
| **Pelvic location of local recurrence (intra-pelvic compartments)** | n = 29 |
| Infralevator | 19 (66 %) |
| Infralevator + Central | 4 (14 %) |
| Central | 4 (14 %) |
| Central + Anterior below PR | 1 (3 %) |
| Central + Posterior | 1 (3 %) |
| **Local recurrence volume ($cm^3$)** | |
| Median (range) | 5.6 (0.4–353.2) |
| **Lymph node location** | n = 5 |
| Mesorectal lymph nodes | 2 (40 %) |
| Inguinal lymph nodes | 2 (40 %) |
| Internal Iliac lymph nodes | 1 (20 %) |
| **Median time to recurrence (months)** | |
| Median (range) | 21.5 (4.8–85.8) |
| **Treatment of recurrence** | |
| Salvage surgery and/or lymph node dissection[a)] | 24 (77 %) |
| Local excision | 3 (10 %) |
| Palliative treatment or BSC | 4 (13 %) |
| **Synchronous distant failures** | n = 3 |
| Liver | 2 (67 %) |
| Para-aortic lymph nodes | 1 (33 %) |

[a)] In combination with pre-operative chemotherapy (n = 1) and brachytherapy (n = 1).
Abbreviations: n = number, PR = peritoneal reflection, BSC = best supportive care.

**Table 3**
Minimum, mean and maximum dose (median).

| Local recurrence (median dose) | Minimum dose (Gy) (range) | | Mean dose (Gy) (range) | | Maximum dose (Gy) (range) | |
|---|---|---|---|---|---|---|
| Recurrence volume | 62.8 (0–64.1) | | 64.0 (39.6–65.2) | | 65.3 (53.8–68.0) | |
| COM | 63.8 (32.5–65.1) | $p = 0.4^a$ | 64.2 (34.0–65.2) | $p = 1.0^a$ | 64.6 (36.1–65.9) | $p = 0.5^a$ |
| Obs-PO | 63.7 (35.8–65.2) | | 64.1 (39.5–65.4) | | 64.5 (44.6–65.7) | |

[a)] Comparison between COM and obs-PO using Wilcoxon signed-rank test.
One patient had two separate local recurrences; only one local recurrence per patient is included in this analysis.
Abbreviations: COM = centre of mass, Obs-PO = observer-based point of origin, Gy = Gray, LN = lymph node.

approximately 50 % of the co-registrations. The cause of registration problems was not always clear, but in nearly 50 % of the corrections, the poor registration was caused by small and/or poor-quality MRI sequences with limited bone structure for registration. In four cases, it was necessary to change the location of the deformable transferred obs-PO, all four cases were due to changes in bowel lumen.

## 4. Discussion

This study aimed to analyse dose and relation to target volumes of point of origin of LRRs after RT for anal cancer. Using this method, it was possible to analyse the prescribed dose to an estimated point of origin of the LRRs. Results showed that the majority of point of origins were located in the high-dose volume (ITV64) and hence received potentially curative radiation doses. This indicates that the cause of recurrence could originate from radioresistant cancer stem cells rather than geographical misses. This is the first published study to use a point of origin-based method to analyse prescribed dose to LRRs after highly conformal techniques for anal cancer.

In previous studies investigating pattern of failure after IMRT for anal cancer, "volumetric approaches" have been applied, classifying LLRs as either in-field, margin or out-of-field in relation to target volumes [12,13,15,16]. In general, the methodology and definition of recurrence classification vary across these studies, and comparison is difficult. The "volumetric approach" previously used lacks information about dose to the recurrence and is highly dependent on recurrence size and hence the time of diagnosis. Point of origin-based recurrence analysis has previously been used in head and neck cancer to analyse the relation to target volumes [8–11]. However, the point of origin-based method has limitations as well. The centroid-based approach, using a mathematically estimated COM as point of origin is an estimate based on the assumptions of isotropic growth, which may not always be the case, especially in large recurrences. Hence, an obs-PO, based on the

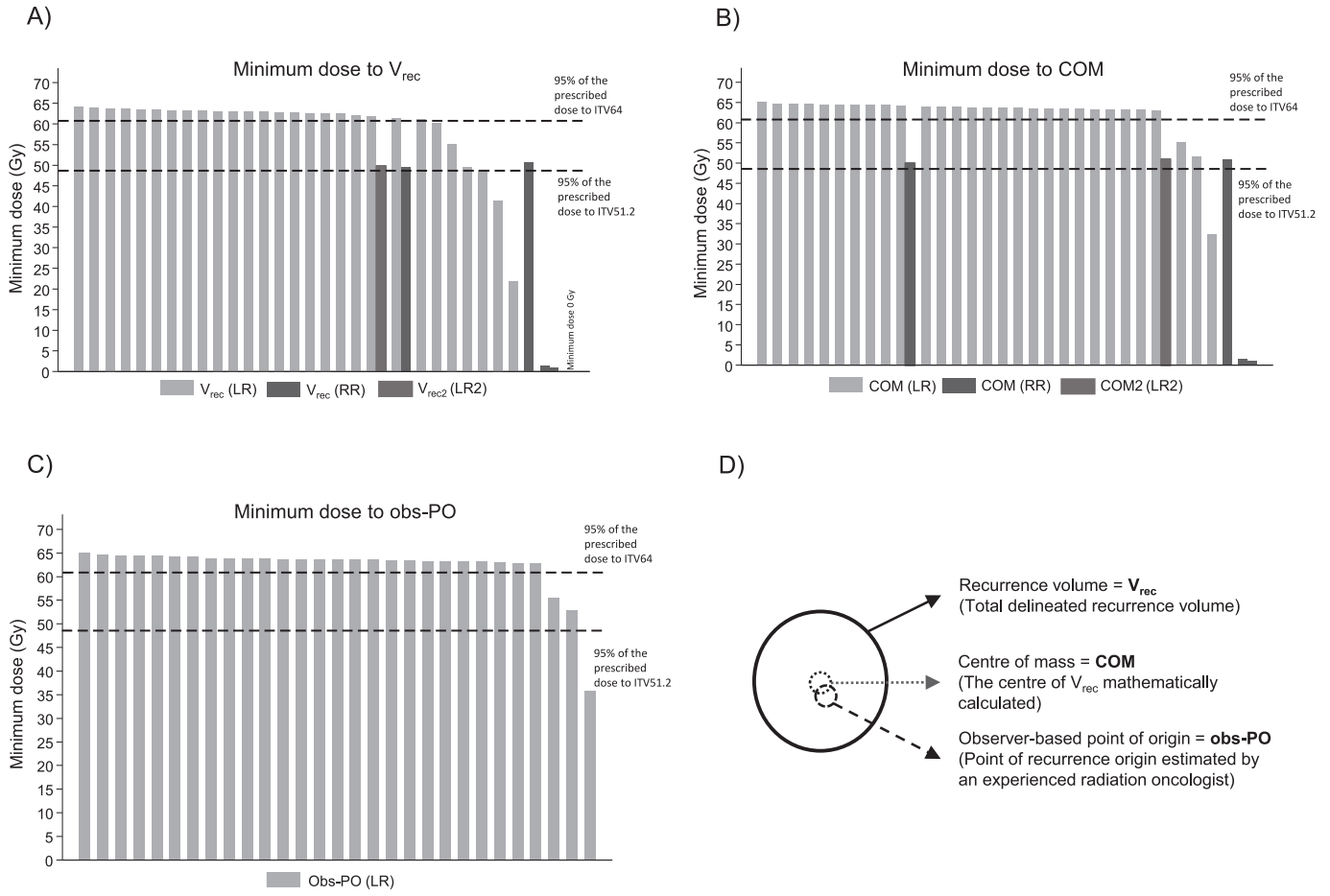


**Fig. 2.** Minimum dose to $V_{rec}$, COM and obs-PO. A-C: Minimum dose to $V_{rec}$, COM and obs-PO. Each bar represents a recurrence. The dashed lines represent 95 % of prescribed dose to ITV64 and ITV51.2. For obs-PO, only LRs are presented. For patients with more than one failure site, each failure is depicted with no space between bars. For COM and $V_{rec}$ one patient is represented with two separate LRs (LR and LR2). D: Definitions of $V_{rec}$, COM and obs-PO. Abbreviations: $V_{rec}$ = recurrence volume, COM = centre of mass, obs-PO = observer-based point of origin, LR = local recurrence, RR = regional lymph node recurrence, ITV = internal target volume.

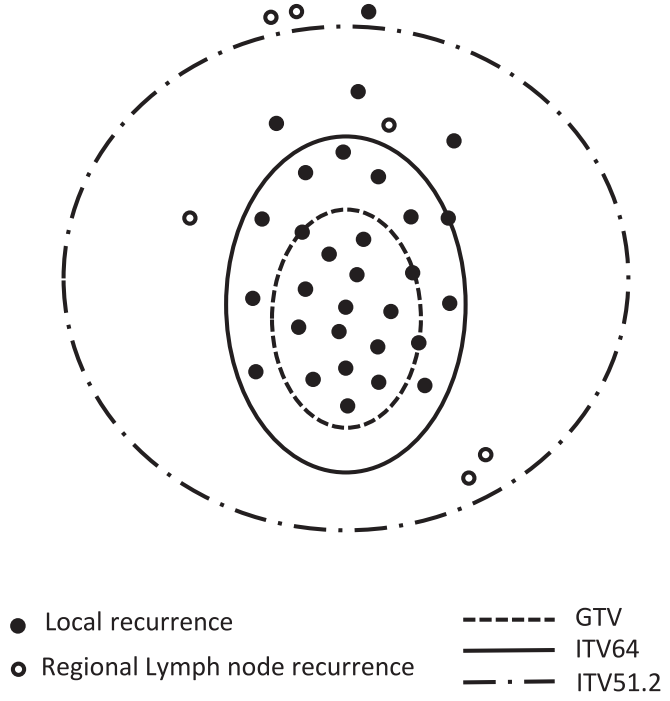


**Fig. 3.** Mapping of COM (loco-regional recurrences) in relation to high dose volume (GTV and ITV64) and elective volume (ITV51.2). Every dot represents one individual loco-regional recurrence (36 individual recurrences (30 local- and 6 regional lymph node recurrences) in 31 patients). If placed on the lines, the COM was included in the volume by less than 100 % but above 0 %. Abbreviations: COM = centre of mass, GTV = gross tumour volume, ITV64 = internal target volume (64 Gy) (high dose volume), ITV51.2 = internal target volume (51.2 Gy) (elective volume).

experience of a radiation oncologist, could be a better estimate. However, this method is by nature observer-dependent and may be more difficult to reproduce and more time-consuming (as an observer need to estimate a point of origin) compared to the COM which is a mathematically estimated point of origin. In head and neck cancer, no relevant clinical differences were found when comparing COM and obs-PO as points of recurrence origin which is in line with our findings [10]. Furthermore, point of origin-based methods are based on the prescribed dose (in our case all patients received the planned number of fractions), which due to differences in e.g., bowel volume, might differ from the actual delivered dose. Since 2010, daily set-up cone beam CT scans have been used in our department, reducing the set-up uncertainties and hence the differences between prescribed and actual delivered dose. However, for all patients in this study, registration of the pelvic bones was used for setup, and the possibility of soft tissue changes can therefore not be eliminated. Dose calculation on cone beam CTs was not possible at the time and calculation of a cumulative dose based on the day-to-day anatomy is therefore extensive and outside the scope of this study. In order to give an estimate of a "worst case"-coverage scenario this study also included estimation of dose to the full recurrence volume ($V_{rec}$). However, this dose estimation is not clinically relevant as the recurrence volume was not present at the time of treatment.

Co-registration in this study was done automatically by the MIM software. We experienced some co-registration difficulties and the necessity for manual adjustments after the RIR, some due to small MRI/poor-quality sequences. Co-registration of time-separated pelvis scans is complicated by few "stable" organs and potentially large differences in bladder- and bowel volumes. In addition, the rMRI was performed with stretched legs, whereas the pCT scan was performed with flexed hips and knees, inducing some variation in hip rotation between scans. The uncertainty of multimodality DIR using the same methods applied in this study has previously been evaluated in head and neck showing a mean distance to agreement of 1.2 to 2.2 mm [22]. The same validation is missing for pelvic multimodality DIR. However, the sphere of 2.5 mm added for dose calculations would allow for minor uncertainties. As a reassurance step visual inspection of both the RIR and DIR was incorporated into the workflow to minimize co-registration uncertainties.

Biological features influencing radiosensitivity might play an essential role in understanding treatment failures but are sparsely investigated in anal cancer. Radioresistant cancer stem cells may not be the only factor influencing response to RT. Human papillomavirus (HPV)-negative cancer cells have been shown to be less radiosensitive compared to HPV-positive cancer cells [23], and HPV-negative anal cancer is known to have a poorer outcome compared to HPV-positive [24]. Nevertheless, of the 31 patients in our study population, 45 % were evaluated for p16 expression, with only one patient diagnosed with an HPV-negative tumour. Even though p16 evaluation was not available in the entire cohort, this emphasises the role of other biological features to help clarify the cause of radioresistance in anal cancer. Hypoxia is associated with increased radioresistance in solid tumours [25] and might play a role in explaining radioresistance in anal cancer [26]. Investigating the biological features, for a better understanding of radioresistance and treatment failure, is highly relevant for developing new intensified treatment options. In light of ongoing dose escalation and de-escalation trials in anal cancer [27], a detailed analysis of the pattern of failure in relation to dose is highly relevant as large dose spans will be seen.

In conclusion, the majority of LRs originated in the high-dose volume (ITV64). No difference in median minimum dose to COM and obs-PO for LRs was observed, and median distance between these points was 3.3 mm, suggesting that a mathematically based, less time-consuming, approach using COM is reasonable in anal cancer. Using a point of origin-based workflow to extract dose to LRRs is feasible, and information is relevant for future treatment optimisation and evaluation.

## 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.phro.2023.100424.

## References

[1] Rao S, Guren MG, Khan K, Brown G, Renehan AG, Steigen SE, et al. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32:1087–100. https://doi.org/10.1016/J.ANNONC.2021.06.015.
[2] Glynne-Jones R, Tan D, Hughes R, Hoskin P. Squamous-cell carcinoma of the anus: progress in radiotherapy treatment. Nat Rev Clin Oncol 2016.447–59.;2016(137):13. https://doi.org/10.1038/nrclinonc.2015.218.
[3] Kachnic LA, Winter KA, Myerson RJ, Goodyear MD, Abitbol AA, Streeter OE, et al. Long-Term Outcomes of NRG Oncology/RTOG 0529: A Phase 2 Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination With 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Anal Canal Cancer. Int J Radiat Oncol Biol Phys 2022;112:146–57. https://doi.org/10.1016/J.IJROBP.2021.08.008.
[4] Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB, Thomas Jr CR, et al. Fluorouracil, mitomycin, and radiotherapy vs. fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal - A Randomized Controlled Trial. J Am Med Assoc 2008;299:1914–21. https://doi.org/10.1007/s10350-008-9429-7.
[5] UKCCCR Anal Cancer Working Party. Epidermoid anal cancer: Results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. Lancet 1996;348:1049–54. https://doi.org/10.1016/S0140-6736(96)03409-5.
[6] Leon O, Guren M, Hagberg O, Glimelius B, Dahl O, Havsteen H, et al. Anal carcinoma - Survival and recurrence in a large cohort of patients treated according to Nordic guidelines. Radiother Oncol 2014;113:352–8. https://doi.org/10.1016/j.radonc.2014.10.002.

[7] Baumann M, Krause M, Hill R. Exploring the role of cancer stem cells in radioresistance. Nat Rev Cancer 2008;8:545–54. https://doi.org/10.1038/nrc2419.
[8] Raktoe SAS, Dehnad H, Raaijmakers CPJ, Braunius W, Terhaard CHJ. Origin of Tumor Recurrence After Intensity Modulated Radiation Therapy for Oropharyngeal Squamous Cell Carcinoma. Int J Radiat Oncol 2013;85:136–41. https://doi.org/10.1016/J.IJROBP.2012.02.042.
[9] Mohamed ASR, Rosenthal DI, Awan MJ, Garden AS, Kocak-Uzel E, Belal AM, et al. Methodology for analysis and reporting patterns of failure in the Era of IMRT: Head and neck cancer applications. Radiat Oncol 2016;11:95. https://doi.org/10.1186/S13014-016-0678-7.
[10] Zukauskaite R, Hansen CR, Brink C, Johansen J, Asmussen JT, Grau C, et al. Analysis of CT-verified loco-regional recurrences after definitive IMRT for HNSCC using site of origin estimation methods. Acta Oncol 2017;56:1554–61. https://doi.org/10.1080/0284186X.2017.1346384.
[11] Due AK, Vogelius IR, Aznar MC, Bentzen SM, Berthelsen AK, Korreman SS, et al. Methods for estimating the site of origin of locoregional recurrence in head and neck squamous cell carcinoma. Strahlenther Onkol 2012;188:671–6. https://doi.org/10.1007/S00066-012-0127-Y/FIGURES/5.
[12] de Meric de Bellefon M, Lemanski C, Castan F, Samalin E, Mazard T, Lenglet A, et al. Long-term follow-up experience in anal canal cancer treated with Intensity-Modulated Radiation Therapy: Clinical outcomes, patterns of relapse and predictors of failure. Radiother Oncol 2020;144:141–7. doi: 10.1016/j.radonc.2019.11.016.
[13] Rouard N, Peiffert D, Rio E, Mahé MA, Delpon G, Marchesi V, et al. Intensity-modulated radiation therapy of anal squamous cell carcinoma: Relationship between delineation quality and regional recurrence. Radiother Oncol 2019;131:93–100. https://doi.org/10.1016/J.RADONC.2018.10.021.
[14] Wright JL, Patil SM, Temple LKF, Minsky BD, Saltz LB, Goodman KA. Squamous cell carcinoma of the anal canal: patterns and predictors of failure and implications for intensity-modulated radiation treatment planning. Int J Radiat Oncol Biol Phys 2010;78:1064–72. https://doi.org/10.1016/j.ijrobp.2009.09.029.
[15] Nilsson MP, Nilsson ED, Johnsson A, Leon O, Gunnlaugsson A, Scherman J. Patterns of recurrence in anal cancer: A detailed analysis. Radiat Oncol 2020;15:1–10. https://doi.org/10.1186/s13014-020-01567-7.
[16] Shakir R, Adams R, Cooper R, Downing A, Geh I, Gilbert D, et al. Patterns and Predictors of Relapse Following Radical Chemoradiation Therapy Delivered Using Intensity Modulated Radiation Therapy With a Simultaneous Integrated Boost in Anal Squamous Cell Carcinoma. Int J Radiat Oncol Biol Phys 2020;106:329–39. https://doi.org/10.1016/j.ijrobp.2019.10.016.
[17] Das P, Bhatia S, Eng C, Ajani JA, Skibber JM, Rodriguez-Bigas MA, et al. Predictors and patterns of recurrence after definitive chemoradiation for anal cancer. Int J Radiat Oncol Biol Phys 2007;68:794–800. https://doi.org/10.1016/j.ijrobp.2006.12.052.
[18] Union for International Cancer Control (UICC). TNM Classification of Malignant Tumours. 8th ed. Oxford: John Wiley & Sons, Ltd; 2017.
[19] PelvEx Collaborative. Minimum standards of pelvic exenterative practice: PelvEx Collaborative guideline. Br J Surg 2022;19:1251–63. doi: doi.org/10.1093/bjs/znac317.
[20] Knöös T, Wieslander E, Cozzi L, Brink C, Fogliata A, Albers D, et al. Comparison of dose calculation algorithms for treatment planning in external photon beam therapy for clinical situations. Phys Med Biol 2006;51:5785. https://doi.org/10.1088/0031-9155/51/22/005.
[21] Piper JW, Richmond J, Nelson AS. VoxAlign Deformation Engine [White Paper]. MIM Softw Publ 2018:1–3.
[22] Kristensen MH, Hansen CR, Zukauskaite R, Johansen J, Samsøe E, Maare C, et al. Co-registration of radiotherapy planning and recurrence scans with different imaging modalities in head and neck cancer. Phys Imaging Radiat Oncol 2022;23:80–4. https://doi.org/10.1016/J.PHRO.2022.06.012.
[23] Sørensen BS, Busk M, Olthof N, Speel EJ, Horsman MR, Alsner J, et al. Radiosensitivity and effect of hypoxia in HPV positive head and neck cancer cells. Radiother Oncol 2013;108:500–5. https://doi.org/10.1016/J.RADONC.2013.06.011.
[24] Serup-Hansen E, Linnemann D, Skovrider-Ruminski W, Hgødall E, Geertsen PF, Havsteen H. Human papillomavirus genotyping and p16 expression as prognostic factors for patients with American Joint Committee on Cancer stages I to III carcinoma of the anal canal. J Clin Oncol 2014;32:1812–7. https://doi.org/10.1200/JCO.2013.52.3464.
[25] Overgaard J. Hypoxic radiosensitization: Adored and ignored. J Clin Oncol 2007;25:4066–74. https://doi.org/10.1200/JCO.2007.12.7878.
[26] Lefèvre AC, Alsner J, Sørensen BS, Tramm T, Toustrup K, Overgaard J, et al. Hypoxia and local tumour control in squamous cell carcinoma of the anus - a hypothesis-generating study. Acta Oncol 2022;61:1132–5. https://doi.org/10.1080/0284186X.2022.2089591.
[27] Sebag-Montefiore D, Adams R, Bell S, Berkman L, Gilbert DC, Glynne-Jones R, et al. The Development of an Umbrella Trial (PLATO) to Address Radiation Therapy Dose Questions in the Locoregional Management of Squamous Cell Carcinoma of the Anus. Int J Radiat Oncol Biol Phys 2016;96:E164–5. https://doi.org/10.1016/J.IJROBP.2016.06.1006.