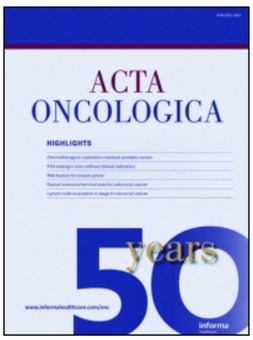

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ORIGINAL ARTICLE

# Dosimetric quantification of the incidental irradiation of the 'true' (deep) ano-inguinal lymphatic drainage of anal cancer patients not described in conventional contouring guidelines

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**ABSTRACT**

**Introduction:** The ano-inguinal lymphatic drainage (AILD) is located in the subcutaneous adipose tissue of the proximal medial thigh. Findings from fluorescence methods give us new information about anatomical conditions of the AILD. Current contouring guidelines do not advise the inclusion of the 'true' AILD into the clinical target volume (CTV). Aim of this work was the retrospective analysis of the incidental dose to the AILD in an anal cancer (AC) patient cohort who underwent definitive chemoradiation (CRT) therapy with Volumetric Arc Therapy – Intensity Modulated Radiation Therapy (VMAT-IMRT).

**Methods:** VMAT-IMRT plans of 15 AC patients were analyzed. Based on findings from new fluorescence methods we created a new volume, the expected AILD. The examined dosimetric parameters were the minimal, maximal and mean dose and V10–V50 that were delivered to the AILD, respectively.

**Results:** The median volume of AILD was 1047 $cm^3$. Mean $D_{min}$, $D_{max}$ and $D_{mean}$ were 7.5 Gy, 58.9 Gy and 40.8 Gy for AILD. The clinical relevant dose of 30.0 Gray covered in mean 76% of the volume of the AILD, respectively.

**Conclusions:** Only 76% of the AILD-volume received at least an expected required treatment dose of 30 Gy incidentally. Concerning the low number of loco-regional relapses in AC patients after definitive CRT one has to balance increased side effects against a rigid oncological–anatomical interpretation of the local lymphatic drainage by including the AILD into the standard CTV.

**Abbreviations:** 2D/3D: 2/3 dimensional; AC: Anal cancer; AILD: Ano-inguinal lymphatic drainage; AP-PA: Anteroposterior-posteroanterior; BSA: Body surface area; CRT: Chemoradiation therapy; CTV: Clinical target volume; Gy: Gray; IMRT: Intensity modulated radiotherapy; PET: Positron Emission Tomography; PTV: Planning target volume; SIB: Simultaneously integrated boost; VMAT: Volumetric modulated arc therapy

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## Introduction

The lymphatic drainage of the anal-canal and the anal-margin is complex and detailed anatomical descriptions are rare and inconsistent. The section above the linea dentata is characterized by perirectal, pelvic and paravertebral lymphatic drainage. Below the linea dentata, especially from the outer section of the anus, the lymphatic drainage follows the medial superficial inguinal lymph nodes [1]. New fluorescence-imaging methods have helped us to define the area of the ano-inguinal lymphatic drainage (AILD) in real-time and transcutaneously [2,3]. Large randomized controlled trials have confirmed a combined chemoradiation (CRT) protocol as a standard treatment for loco-regionally advanced squamous-cell anal cancer (AC) patients [4,5]. Standard contouring guidelines recommend an inclusion of the primary tumor with a 2.5 cm margin into the target volume (CTV). The RTOG Consensus Panel felt that elective coverage of the inguinal and external iliac regions should be routine for anal carcinoma. The recommended extent of the inguinal region (CTV) should be 2 cm caudal to the saphenous/femoral junction [6]. Lee and Lu [7] recommend an elective irradiation of uninvolved inguinal nodes (CTV low risk). Ultimately, up to now there are no recommendations of inclusion of the ano-inguinal drainage (AILD) into the clinical target volume (CTV) by any contouring guidelines.

Anal cancer is a relatively rare disease. The incidence in the US and death rates for women are 2.1 and 0.3 of 100.000 while they are 1.6 and 0.2 of 100.000 for man [8]. Currently, Intensity modulated radiotherapy (IMRT) should be the standard for radiation treatment of AC patients [6]. Several studies have shown the importance of elective groin irradiation especially for T3–T4 tumors. Among patients with uninvolved

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inguinal nodes at diagnosis who did not receive elective radiation to the groin the inguinal recurrence rates for T1–2N0 tumors range from 5% to 13%, while for T3–4N0 tumors it is 6–30% [9–13]. Matthews et al. prematurely closed a study (T1–2N0, no radiation to the groins) because of an unacceptable high inguinal relapse of 22.5% after three years [14].

In the connection with the experience of marginal misses in IMRT-treated AC patients due to misunderstandings of anatomical conditions (e.g., perirectal and presacral) [15], a strict evaluation of the correlation of anatomical condition with the target volume definition seems warranted. Because of the new anatomical understanding of the AILD and the high number of inguinal recurrence in untreated groins and a low but reasonable number of inguinal recurrence in treated groins in locally advanced AC patients we have performed a retrospective analysis of the incidental dose to the AILD in an AC patient cohort who underwent definitive CRT with Volumetric Arc Therapy – Intensity Modulated Radiation Therapy (VMAT-IMRT) and using structure sets according to current guidelines.

## Methods

### *Radiation technic details*

A total of 15 VMAT-IMRT plans of AC patients treated from 2010 to 2016 were analyzed. Eleven patients were treated on a Varian Clinac® DHX linear accelerator (Varian Medical Systems, Palo Alto, CA, USA) using IGRT (image-guided radiotherapy) with kilo-voltage cone-beam-CT scans (CBCT). Patients regularly received three arcs in the main plan and two arcs for each boost plan (6 or 15 MV). Four patients received TOMO-therapy with the TomoTherapy Hi-ART-System (6 MV) (Accuray, Sunnyvale, CA, USA). We used the Eclipse 13.0 Treatment Planning System (Varian Medical Systems, Palo Alto, CA, USA) for contouring and dose comparison. Contouring was performed on planning CTs with 3 mm slice thickness. For the definition of the target volumes we also used MRI-scans of all patients and a PET-CT scan for eight patients. The dose was prescribed of the median. The 11 patients with positive lymph nodes received either a sequential boost (7) or a simultaneous integrated boost (SIB) (4).

Dose constraints for organs at risk (OAR) (rectum, sigmoid, small bowel, femoral head left and right, penis/scrotum or vagina/vulva, skin of AILD, urinary bladder) orientated on Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) [16].

### *Definition of the AILD*

With these radiation plans we created a new volume, the expected ano-inguinal lymph drainage (AILD). These lymph vessels are usually not detectable by standard lymphangiography [17–22]. Therefore, the true or real location of the AILD had until now not exactly been known and further seems to differ with each individual. Some authors believe in an AILD through the obturator foramina, others mention a direct drainage via the soft tissue of the ischio-anal fossa [14]. However, in recent years new fluorescence-imaging methods like the indocyanine-green-method corroborate the fact, that this AILD forms a network of very thin vessels and is located in the subcutaneous adipose tissue of the medial thigh. This network is widely disseminated and can reach some cm below the anus (Figure 1A) [2,3].

Based on anatomical descriptions and these new images of fluorescence-imaging methods, we connected the soft tissue between the anus and the inguinal vessels with the following demarcations: The caudal demarcation was defined 2 cm below the trochanter minus or at least 2.5 cm below the anal margin. The cranial end of AILD was at the level of the symphysis (anal) or where no more soft tissue connection between anus and inguinal could be identified (inguinal). Ventral demarcation was the femoral skin; dorsal was the transition of the gluteal muscles to the subcutaneous adipose tissue. The lateral demarcations were the adductor muscles

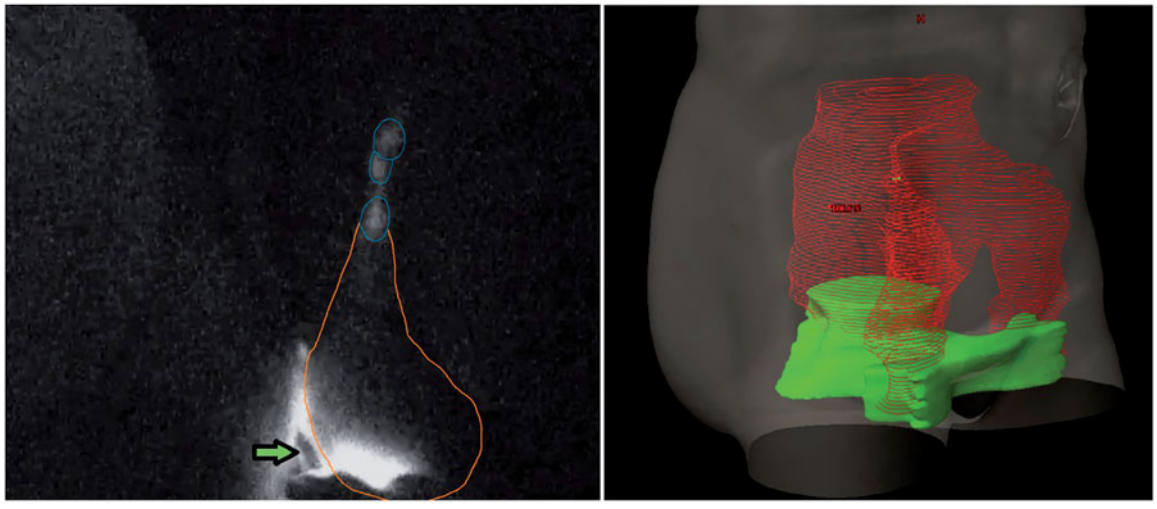

**Figure 1.** (A) Oblique view on the perineum and left leg during fluorescence-imaging of an anal cancer patient in lithotomy position. The indocyanine-green was injected along the anal verge (green arrow) to detect the ano-inguinal lymphatic drainage (orange) and the inguinal sentinel lymph nodes on the left groin (blue). (B) Lateral oblique view on the pelvis. Expected ano-inguinal lymphatic drainage (green) in relation to the previous PTV (spirally red) in an anal cancer patient treated with VMAT-IMRT.

(anal) and the medial femur bone or at least 0.5 cm around femoral vessels (inguinal) (Figure 1B).

### Dosimetric evaluation

We examined dose parameters (minimum, maximum, median, V10, V20, V30, V40, V45, and V50) that were delivered to the AILD target volume, the AILD outside of the previous PTV (AILD-PTV) and of the mean and mean maximum dose of the organs at risk as represented in the dose-volume histogram (DVH).

## Results

### Analysis of patients, treatment details and basic dosimetric parameters

From 15 AC patients, 10 (67%) were female and 5 (33%) were male. The mean age was 62 years (45–77). All patients had squamous cell carcinoma histology. Patients mainly had T2 (47%) and N2 (47%) disease while 73% had positive nodes before treatment. The predominant UICC-Stadium was IIIB (60%). All patients received simultaneous chemotherapy similar to the RTOG 98-11 with two cycles of Mitomycin on day 1 and 29 with 10 mg/qm BSA (max. 20 mg per cycles) and two cycles of 5-Fluoruracil on day 1–4 and 29–32 with 1000 mg/qm BSA) or Capecitabine (825 mg/qm BSA two times a day only on days of RTx). Depending on the nodal status and tumor extension the mean dose for the inguinal LAW was 44.8 Gy (36.0–50.4 Gy), for the pelvic LAW it was 50.1 Gy (45.0–55.8 Gy) and for the primary tumor side it was 56.6 Gy (50.4–59.4 Gy). Regions with macroscopic disease received at least 50.4 Gy (mainly >54 Gy). The single doses ranged from 1.6 Gy to 2.0 Gy. At the beginning of radiation therapy 11 of 15 patients had positive lymph nodes. Nine patients had positive nodes on pelvic site (five mesorectal, three internal iliac, two external iliac), two on inguinal site and four on both sites. Seven of these patients were treated by a sequential boost with a mean dose of 7.9 Gy (5.4–14.4 Gy). Four patients had a simultaneous integrated boost (SIB) with a mean dose of 6.9 Gy (5–9 Gy). The single dose of the SIB-volumes was 2.13 Gy (2.00–2.25 Gy).

The mean dose on the femoral head was 32.0 Gy, for the small bowel it was 14.3 Gy, for the bladder it was 36.7 Gy and for the skin in the area of AILD it was 29.6 Gy. Dose statistics for other organs at risk can be found in Table 1.

### AILD analysis

The median volume of AILD and AILD-PTV was 1047 $cm^3$ (643–1391 $cm^3$) and 656 $cm^3$ (415–1219 $cm^3$), respectively. Mean $D_{min}$, $D_{max}$ and $D_{mean}$ were 7.5 Gy (0.1–22.9 Gy), 58.9 Gy (53.1–63.0 Gy) and 40.8 Gy (26.7–47.6 Gy) for AILD and 7.5 Gy (0.1–22.9 Gy), 56.5 Gy (52.1–61.6 Gy) and 33.6 Gy (20.7–41.3 Gy) for AILD-PTV, respectively. Nearly the whole volume of AILD and AILD-PTV received 10.0 Gray (mean V10: 96% and 94%), respectively. The clinical relevant dose of 30.0 Gray covered in mean 76% of the volume of the AILD and just 64% of the AILD-PTV, respectively. The V50 of the AILD and AILD-PTV (volume almost completely overlapping with the previous PTV) was in mean 35% and 9%, respectively. The Mean V10, V20, V30, V40, V45, V50 for AILD and for the AILD-PTV are shown in Table 1.

**Table 1.** Dose statistics (means values) of 15 anal-cancer patients treated by IMRT-VMAT

| | | Dose | | |
|---|---|---|---|---|
| Structure | | Min (Gy) | Mean (Gy) | Max (Gy) |
| Primary tumour | | 50.4 | 56.6 | 59.4 |
| Inguinal lymph nodes | | 36.0 | 44.8 | 50.4 |
| Pelvic lymph nodes | | 45.0 | 50.1 | 55.8 |
| AILD | | 7.5 | 40.8 | 58.9 |
| AILD - PTV | | 7.5 | 33.6 | 56.5 |
| Urinary Bladder | | | 36.0 | 55.1 |
| Femoral head r. | | | 31.5 | 47.1 |
| Femoral head l. | | | 32.4 | 46.2 |
| Vagina/ Vulva | | | 32.6 | 52.1 |
| Penis | | | 25.6 | 40.0 |
| Scrotum | | | 14.4 | 37.7 |
| Skin AILD | | | 29.6 | 49.7 |
| Rectum | | | 55.5 | 58.8 |
| Sigmoid | | | 46.0 | 54.6 |
| Intestine | | | 14.3 | 54.1 |
| | | Volume | | |
| Structure | | Min (%) | Mean (%) | Max (%) |
| AILD | V10Gy | 76.2 | 95.7 | 100 |
| | V20Gy | 60.0 | 87.4 | 100 |
| | V30Gy | 43.0 | 76.4 | 97.5 |
| | V40Gy | 28.9 | 60.0 | 80.5 |
| | V45Gy | 21.8 | 49.0 | 69.1 |
| | V50Gy | 10.1 | 34.6 | 52.0 |
| AILD - PTV | V10Gy | 69.8 | 94.1 | 100 |
| | V20Gy | 49.3 | 81.5 | 100 |
| | V30Gy | 27.6 | 64.0 | 95.5 |
| | V40Gy | 9.8 | 36.6 | 61.0 |
| | V45Gy | 2.3 | 22.8 | 41.1 |
| | V50Gy | 0.1 | 8.9 | 27.5 |

For those four patients treated by Tomotherapy mean $D_{min}$, $D_{max}$ and $D_{mean}$ were 16.3 Gy (9.3–22.9 Gy), 59.5 Gy (55.9–62.5 Gy) and 46.2 Gy (44.5–47.6 Gy) for AILD and 16.3 Gy (9.3–22.9 Gy), 58.8 Gy (55.8–61.6 Gy) and 39.3 Gy (34.7–42.0 Gy) for AILD-PTV, respectively. The V50, V30 and V10 was 43.4% (38.4–49.6%), 89.9% (76.1–97.5%) and 100% for the AILD and 15.0% (11.6–18.7%), 81.9% (58.3–95.5%) and 100% for the AILD-PTV, respectively.

## Discussion

We found that for IMRT-treated patients with AC the Mean V10, V20, V30, V40, V45 and V50 of the volume of the AILD was 96%, 87%, 76%, 60%, 49% and 35%, respectively.

Aim of this work was the retrospective analysis of the incidental dose to the 'true' AILD in an AC patient cohort who underwent definitive CRT with VMAT-IMRT because contouring guidelines currently does not recommend an inclusion of the AILD (connection of the CTV from the anus to the inguinal nodes) into the target volume. The RTOG 98-11 trial used 30.6 Gy as a prophylactic treatment dose of the groin in patients with uninvolved inguinal nodes before the treatment [4]. Therefore, we think that at least 30 Gy is a reasonable dose for prophylactic treatment for potential

micro metastasis in uninvolved inguinal nodes. In our analysis at least 76% of the volume of the expected AILD received at least an expected required treatment dose of 30 Gy incidentally. Under consideration of the V30 of AILD-PTV (64%) and the anatomical conditions (Figure 1) especially the caudal parts of the created volumes, with a clear distance to the previous PTV, received an inadequate prophylactic treatment dose (Figure 2). However, new fluorescence-imaging methods have shown the area of the AILD transcutaneously, the variation of anatomical circumstances in different individuals and anatomical details of the AILD remain uncertain. For a further understanding of the AILD, basic research for example with MRI-lymphangiography of AC patients is needed.

To evaluate the clinical need for inclusion of the 'true' AILD, the expected toxic effects and current inguinal failure rates after radiotherapy to the groins must also be considered. Next to tumor extension at diagnosis, nodal status has been identified as one of the most important prognostic factors. Tumors >5 cm and positive lymph nodes at diagnosis have a significant correlation with poor five-year disease-free survival and five-year overall survival. About 10–25% of all AC patients presents with synchronous and 5–25% with metachronous inguinal lymph node metastasis [23–25]. After primary CRT the RTOG 98-11 reported a regional failure rate of 7% after three years but 25% after five years [4]. Unfortunately, the major prospective studies (ACT II, RTOG 98-11) did not report the relapse rates on the inguinal side. Most IMRT-studies have shown high locoregional control rates after treatment of the groin as compared to 3D-RT [26,27]. In a study of Tomasoa et al. 4 of 106 patients (3.7%) presented inguinal lymphonodal recurrence after IMRT although the groin was part of the target volume. Three of these patients had initial inguinal involvement [28]. Unfortunately the total number of initial inguinal involvement of the 106 patients could not be developed. Furthermore Tomasoa et al. mentions that inguinal failure rates with IMRT is comparable with 3D-treated patients of Das et al. (the chance of local recurrence on inguinal side was almost 0% (0.6–1.6%) [11,29].

Scher et al. [30] summarized eight IMRT-studies which presented the dermatological toxicity after radiation of AC patients ($n = 39$–78). These patients received mainly 45 Gy to the uninvolved lymph nodes. Grad ≥3 dermatological toxicity ranged from 0% to 42% (mean: 23%). The RTOG 0529 study has shown significance reduced grade ≥3 dermatologic AEs, 23% compared with RTOG 98-11 with 49% ($P < 0.0001$) [31]. In our study the mean dose in the overlapping area of the skin with the AILD was 29.6 Gy, respectively. By including the AILD in the target volume we would expect a slight increase of dose, but an increased skin-size which would be affected. We don't expect any significant increase of dose to the femoral head, however we expect the genital region to be significantly affected.

Concerning applied radiotherapy techniques, large prospective trials (RTOG 98-11, ACT II) used anteroposterior–posteroanterior (AP-PA) or multifield techniques. With 2/3-D technics bigger parts of the AILD usually could have been fitted into the AP-PA fields (except for the caudal parts) and received at least 30.6 Gy. At RTOG 98-11 the inferior border was the anus with a minimum margin of 2.5 cm around the anus and tumor [2,3]. The advantage of IMRT-technics is shown in the first prospective IMRT-trial for AC. The RTOG 0529 reported less Grad ≥3 dermatology and gastrointestinal toxicity (both 21%) than RTOG 98-11 with 2/3D-RT technics

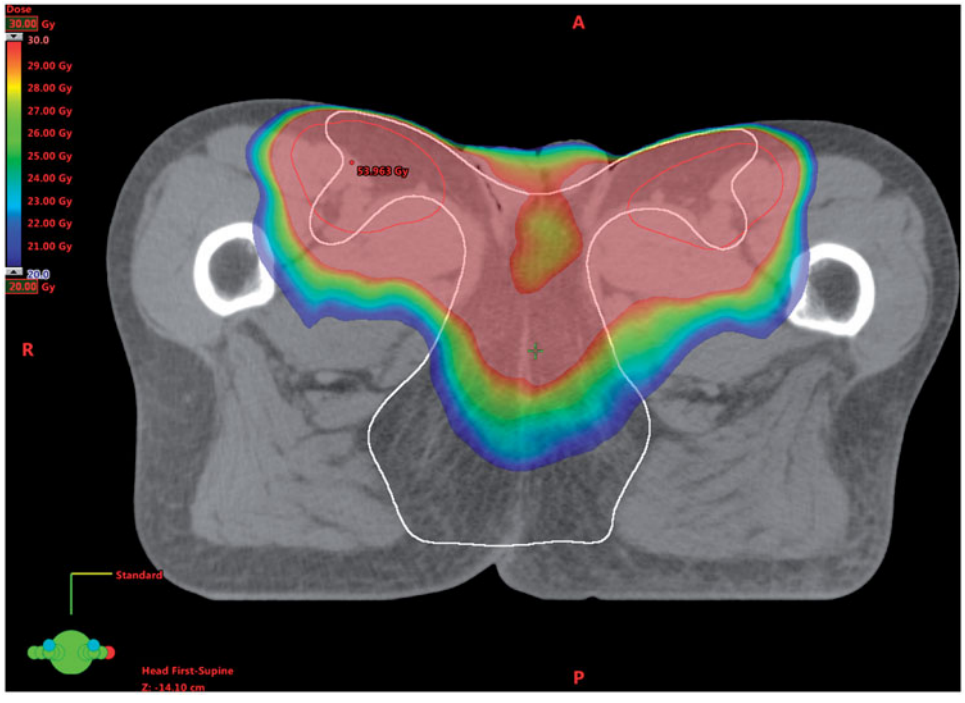


**Figure 2.** Axial CT slice of an anal cancer patient 1.2 cm caudal to the previous PTV. The 20–30 Gy is represented in colorwash. The dorsal parts of the ano-inguinal lymphatic drainage (yellow) are not sufficiently covered by the 30 Gy isodose (red colorwash).

(47% and 36%) [31]. To assess the risk for increased dermatological and genital toxicity by including the AILD into the target volume, we will perform a NTCP-based dose distribution analysis in the area of AILD on 3D-plans compared with IMRT-plans.

In summary, an evaluation of the inguinal recurrences with the initial tumor stage as well as the tumor localization is necessary in order to evaluate the benefit of encompassing the AILD into the CTV. Because of the low incidence of AC and low risk of inguinal recurrence this seems to be a difficult to implement.

## Conclusions

At least 76% of the AILD-volume received at least an expected required treatment dose of 30 Gy incidentally. However, especially caudal of the created volumes, with a clear distance to the previous PTVs, received an inadequate therapeutic dose. Concerning the low number of locoregional relapses in AC patients after definitive CRT one has to balance increased skin side effects against a rigid oncological–anatomical interpretation of the local lymphatic drainage by including the AILD into the standard CTV. For high-risk patients for inguinal recurrence (T4, inguinal involvement/N3, anal margin) a consequently radiation of the AILD could be useful. To answer this question we need both, a better anatomical understanding of the true AILD (e.g., MRI lymphangiography) and a strict correlation of the tumor stage and site with inguinal recurrence in IMRT treated patient cohort.

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