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Clinical Investigation

Recommendations and Clinical Validation of Inguinal Clinical Target Volume Delineation in Penile Cancer

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Purpose: This study determined the patterns of distribution of inguinal nodes and the optimal margin needed around the femoral vessels to propose guidelines for inguinal clinical target volume (CTV) delineation in penile cancer.

Methods and Materials: Patients with biopsy-proven penile squamous cell carcinoma with inguinal node metastases were identified on a computed tomography scan. Distribution of nodes and distance of nodes to the nearest femoral vessel and inferior edge of pubic symphysis (IPS) were obtained. A 3-dimensional CTV margin to cover 95% of the nodes was estimated to evolve contouring guidelines. A comprehensive contouring guide with a visual atlas for inguinal CTV delineation was created. The proposed CTV was prospectively validated in 14 consecutive patients with penile squamous cell carcinoma treated with post-operative radiation therapy to the inguino-femoral region.

Results: Of the 222 inguinal lymph nodes analyzed in 33 patients, 99% were located anterior (81% antero-medial, 18% antero-lateral) to femoral vessels. A majority (95%) of the antero-laterally located nodes were superior to IPS. Margin around the femoral vessels to cover 95% of the nodes for supra-IPS region in anterior, medial, and lateral directions was 29, 23, and 21 mm, respectively, and for infra-IPS region in anterior and medial directions was 21 and 23 mm, respectively. Cranial and caudal extent of CTV delineation with respect to IPS was at 48 and 50 mm, respectively for 95% nodal coverage. On prospective validation, after a median follow-up of 24 months (range, 5-31), none of the patients developed marginal recurrences. Grade 1 and grade 2 lymphedema was seen in 6 (42.8%) and 4 (28.5%) patients, respectively.

Conclusions: This study analyzed pattern of distribution of inguinal nodes and proposes guidelines for inguinal CTV delineation in penile cancer. The proposed guidelines were validated prospectively in a small cohort of patients and found to be implementable and safe.

Introduction

Penile squamous cell carcinoma (SCC) has high propensity of metastasis to the inguino-femoral lymph node region. The primary lymphatic drainage site is located above and medial to the junction of the epigastric and saphenous veins, which corresponds to the sentinel nodes.[1] The standard management of a clinically positive groin (cN+) is bilateral radical inguinal lymphadenectomy. According to

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National Comprehensive Cancer Network guidelines (V2.2020), adjuvant external beam radiation therapy and/or chemotherapy are indicated if any 1 of the following high-risk features is present: positive surgical margin, pelvic nodal metastasis in $\geq$ 2 nodes, extra capsular extension, bilateral nodal involvement, or $\geq$ 4 cm tumor in lymph nodes. For a clinically negative groin (cN0), surveillance, diagnostic sentinel lymph node biopsy, or modified inguinal lymph node dissection with or without ipsilateral radical inguinal lymphanectomy is considered, depending on risk of involvement of inguinal nodes. Prophylactic external beam radiation therapy can also be given to the inguinofemoral region in cN0 groin.[2-4] An ongoing phase III randomized control trial—InPACT (International Penile Advanced Control Trial)—is exploring the role of neo-adjuvant chemoradiation therapy and adjuvant radiation therapy in locally advanced penile cancer. The results of this study will add robustness to current management.[5]

Conventionally, radiation therapy portals for the inguinofemoral nodal region are defined by bony landmarks, which cause normal tissue toxicity and inadequate coverage, specifically for deep seated nodes.[6] Intensity modulated radiation therapy (IMRT) allows for delivery of highly conformal radiation therapy with excellent coverage of target structures and relative sparing of healthy normal tissue like skin as well as critical adjacent structures like the bowel, bladder, femoral head, neck, and external genitalia.[7] However, use of IMRT requires detailed anatomic knowledge, detailed knowledge of distribution of inguinal nodes in penile cancer, and precise delineation of clinical target volumes (CTVs) and normal tissues to adequately cover areas at risk for disease and reduce dose to normal tissues. With increasing use of IMRT in the treatment of penile cancer, requirement of evidence-based guidelines for inguinal lymph node CTV delineation is crucial. Studies published previously investigating the distribution of inguinal lymph node metastases were of a small sample size and included heterogeneous pelvic malignancies like vulva, distal rectum, anal canal, and distal one-third of vagina, while patients with penile cancer made up less than 2% of the study population.[8-10] Therefore, extrapolating these guidelines of inguinal CTV delineation to penile cancer may not accurately define the region at risk, that is, it may result in inadequate coverage of high-risk areas or over-treat beyond the high-risk areas. The purpose of this study was to determine the distribution of inguinal nodes and optimal margin needed around the femoral vessels for complete inguinal lymph node coverage to propose guidelines for inguinal nodal CTV delineation in a case of penile cancer.

Methods and Materials

Eligibility criteria

After institutional review board approval, patients with biopsy-proven penile SCC with inguinal lymph node metastases at presentation treated between 2014 and 2017 were screened. Inclusion criteria were as follows: Only patients who had a baseline diagnostic contrast enhanced computed tomography (CECT) scan in a digital format were included to identify radiologically positive node/s and their location. The radiological criteria for node positivity were greater than 10 mm in short axis diameter (SAD) irrespective of status of hilum and less than 10-mm SAD but with abnormal features (heterogeneous appearance on a CECT, low density center due to necrosis, loss of fatty hilum, irregular border due to extra capsular extension, round in shape).[11,12] Fine needle aspiration cytology/biopsy from the radiologically positive inguinal nodes was not considered mandatory for inclusion. After ensuring the completeness of the baseline CECT scan up to mid-thigh, individual scan was imported to the Eclipse radiation therapy treatment planning system (TPS) version 13.5.

Contouring femoral vessels, choosing and assigning coordinates to reference point

For every imported scan, bilateral femoral vessels (artery and vein as a single structure) were contoured, with the cranial extent being when it enters the thigh from behind the inguinal ligament (first appearance of head of femur was taken as a bony landmark) up to 3 cm below the greater trochanter, which was taken as the caudal extent of contouring. Inferior edge of pubic symphysis (IPS) was identified on axial CECT scan slices and marked for each scan using a reference marker tool. The values of the x, y, and z coordinate system for each marked point of IPS was identified and noted from the Eclipse TPS version 13.5 for each patient (Fig. 1A).

Locating the nodal center with respect to ipsilateral edge of femoral vessel and the reference point (IPS)

The location of each positive node in axial plane was noted in relation to the closest edge of ipsilateral femoral vessels. SAD in mm was measured for each node on an axial computed tomography (CT) scan slice (Fig. 1B). The radiological center was identified for each positive node and given a unique reference, for example, 12 R N3: patient number 12, right groin, and node number 3 (Fig. 1C). This radiological center was mapped 3-dimensionally (3D) with the x, y, and z coordinate system in the TPS. The location of the center of each node with respect to IPS was noted. The location of nodes was divided into 2 parts; nodes at and superior to the level of IPS (supra-IPS) and nodes inferior to the IPS (infra-IPS) (Fig. 1D). The distance of the center of each positive node in relation to the closest edge of ipsilateral femoral vessel and IPS (both supra- and infra-IPS) was measured in 3D coordinates.

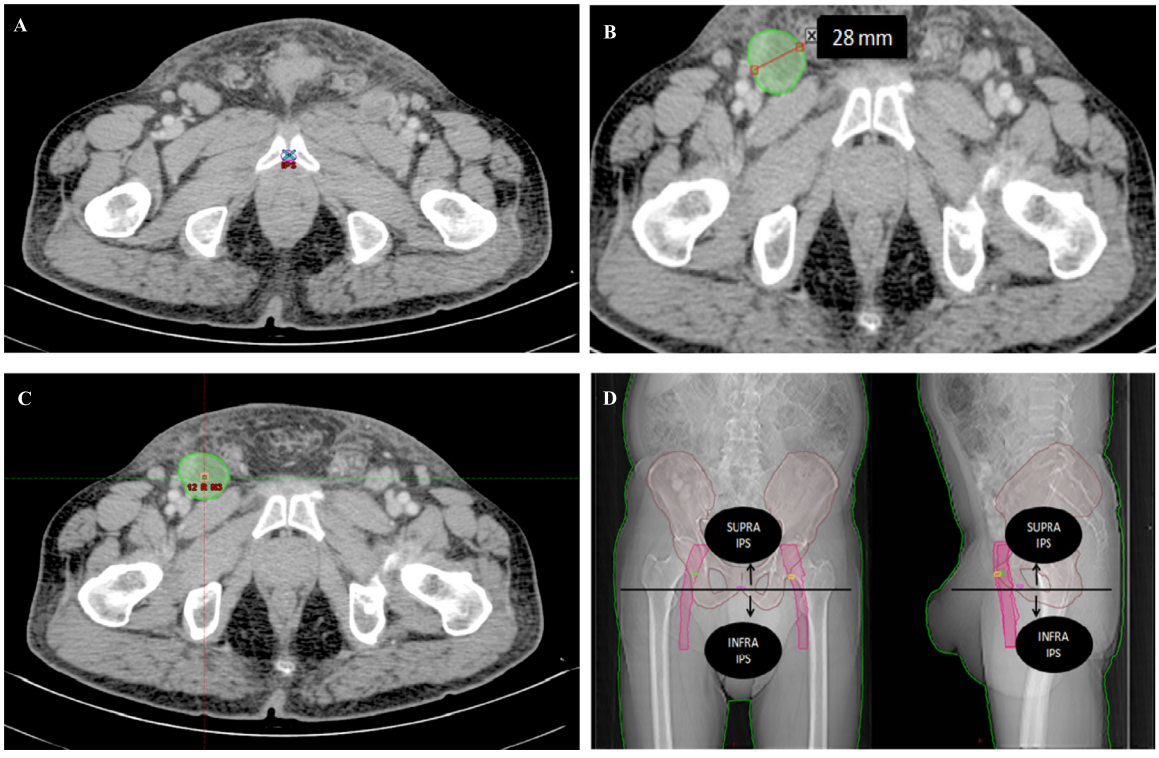


Fig. 1. (A) Marking inferior edge of pubic symphysis (IPS) on an axial computed tomography (CT) scan (**X**). (B) Measuring short axis diameter (SAD) of node. (C) Identification, referencing and marking the nodal center (□). (D) Antero-posterior (AP) and sagittal views showing supra-IPS and infra-IPS regions based on a horizontal line passing through the level of IPS along with bilateral femoral vessels and pubic bone.

Relationship of the individual node with the surrounding structure(s)

The relationship of the individual node was determined with respect to the surrounding structures like skin, muscle, bone, bladder, and spermatic cord.

Estimation of CTV margin and evolving contouring guidelines

In both supra- and infra-IPS regions, margins to cover 90% and 95% of the nodes were obtained in each of the anterior, medial, posterior, and lateral directions with respect to the femoral vessels (mm). The margins to cover 90% and 95% of the nodes in both cranial and caudal extent with respect to the IPS were also obtained (mm). To evolve the contouring guideline, these estimated margins were applied to a reference radiation therapy planning CT scan of a patient with biopsy- proven SCC of penis with non-operated groin and a post-operative groin in the treatment position. On each CT scan, the IPS was identified and bilateral femoral vessels and conventional organs at risk, that is, bladder, rectum, bilateral femoral head and neck, and spermatic cord, were contoured. A 3D CTV margin to cover 95% of the nodes as obtained from the study was grown around the femoral vessels both superiorly and inferiorly taking IPS as the reference point in a patient with a non-operated and post-operative groin as explained earlier. The margins around the femoral vessels were reviewed by the investigators of this study, and the CTV was modified in relation to the previously mentioned surrounding structures including vascular spaces or any other structure(s).

Prospective validation of proposed contouring guidelines

The contouring guidelines for inguinal CTV delineation proposed by the present study were prospectively validated in consecutive patients with SCC of penis treated with post-operative radiation therapy to the groin with or without pelvic radiation therapy. Radiation therapy planning was carried out on CECT scans of 5-mm slice thickness taken from upper border of L2 vertebra up to mid-thigh. All patients were scanned in the supine position. The target volumes included bilateral groin in all patients with or without pelvis. For each patient, IMRT using volumetric arc therapy with 6 MV photons was used for radiation therapy planning, and the total radiation therapy dose delivered was 50 Gy in 25 fractions with 2 Gy per fraction/day given for 5 days a week. Treatment verification was carried out daily for first 3 days of starting radiation therapy followed by weekly using electronic portal imaging device or cone beam CT.

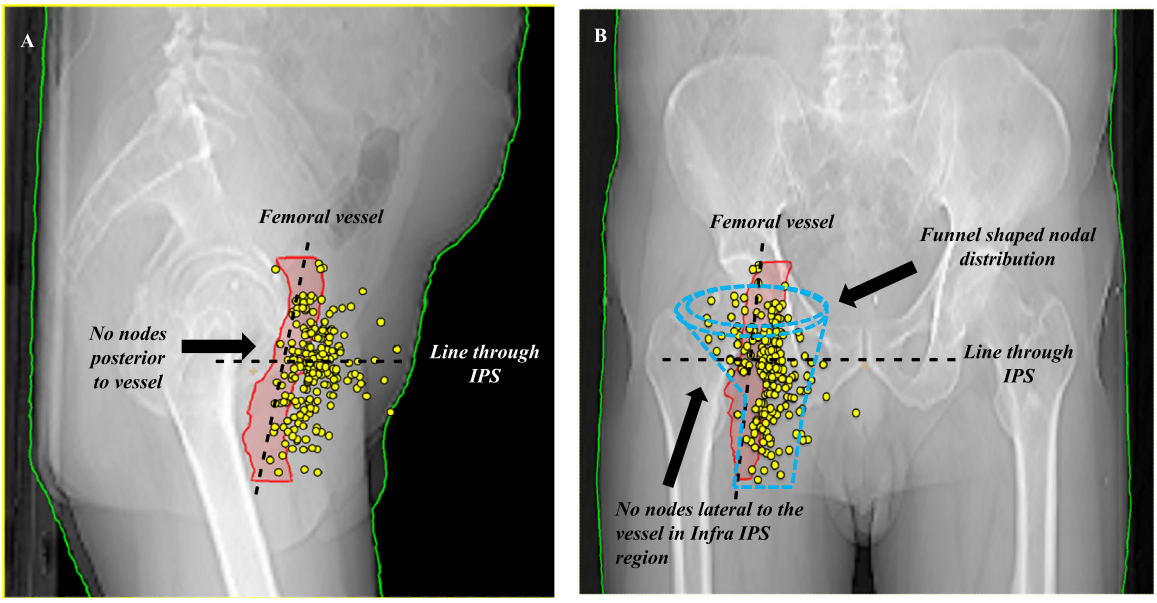


Fig. 2. Distribution of center of each involved inguinal lymph node (yellow) plotted with respect to inferior edge of pubic symphysis (IPS) and right femoral vessel (red). (A) Sagittal section of pelvis and right upper thigh depicting that 99% of the nodes lie anterior to the femoral vessel. (B) Coronal section showing 81% nodes lie antero-medially to the femoral vessel with no nodes seen lateral to the femoral vessel in infra-IPS region (Funnel-shaped nodal distribution).

Patients were followed up every 3 months in the first 2 years, every 6 months in the third and fourth years, and yearly thereafter. Assessment included history, physical examination, ultrasound of abdomen, pelvis, and groin with chest radiograph; and for late radiation toxicity of skin using Radiation Therapy Oncology Group criteria and lymphedema using Common Terminology Criteria for Adverse Events version 4 criteria. A CECT thorax, abdomen, and pelvis was done annually or in cases of suspected recurrence. A recurrence was confirmed with a biopsy/fine needle aspiration cytology whenever feasible.

Results

A total of 222 involved nodes (right groin = 115, left groin = 107) in 33 patients (mean number of nodes in each patient = 6) with biopsy-proven penile cancer were included and analyzed. Median SAD of involved lymph nodes was 19 mm and ranged from 7 to 60 mm.

Location of the involved nodes in relation to the ipsilateral femoral vessel and reference point (IPS)

Ninety-nine percent (220) of the nodes were located anterior to femoral vessels (Fig. 2A), out of which 81% (181) of the nodes were antero-medially and 18% (39) of the nodes were antero-laterally located. Only 1% (2) of the nodes were located postero-medially to the vessel. Of the total 222 nodes, 70% (155) were located superior (147 nodes) and at the level (8 nodes) of IPS. The remaining 30% (67) were located inferior to IPS. A majority (95%) of the antero-laterally located nodes were superior to IPS. No nodes were present antero-laterally to the femoral vessel inferior to the IPS (Fig. 2B).

Distance of the nodes from the nearest ipsilateral edge of femoral vessel and reference point (IPS)

The median - distance between the center of the node to the nearest edge of the ipsilateral femoral vessel was maximum in anterior direction for both supra-IPS region (12 mm; range, 0-42 mm) and infra-IPS region (11 mm; range, 1-23 mm). The median (range) distance of nodes superior to IPS was 20 mm (0-72) and inferior to IPS was 18 mm (1-60) (Table 1).

Margins to cover the nodes around the femoral vessels; superior and inferior to the reference point (IPS)

Margins to cover 90% and 95% of the nodes around femoral vessels are shown in Table 1. For supra-IPS region, maximum margin was needed in the anterior direction (29 mm for 95% coverage). For infra-IPS region, maximum margin was needed in the medial direction (23 mm for 95% coverage). No margin was required posteriorly in supra-IPS and posteriorly and laterally in the infra-IPS region in relation to femoral vessels. Cranial and caudal extent of inguinal CTV

Table 1 Median and range of distance (mm) of nodes from nearest ipsilateral edge of femoral vessel and margins for 90% and 95% nodal coverage (mm) in supra IPS and infra IPS regions

	Supra-IPS			Infra-IPS		
Direction from femoral vessel	Median (range) distance from vessel (mm)	Margin for 90% nodal coverage (mm)	Margin for 95% nodal coverage (mm)	Median (range) distance from vessel (mm)	Margin for 90% nodal coverage (mm)	Margin for 95% nodal coverage (mm)
Anterior	12 (0-43)	22	**29**	11 (1-23)	20	**21**
Medial	7 (2-44)	16	**23**	9 (1-26)	21	**23**
Lateral	5 (2-22)	20	**21**	4 (4-4)	0	**0**
Posterior	2 (2-10)	0	**0**	0	0	**0**

Median and range of distance (mm) of nodes and cranio-caudal extent of contouring from IPS for 90% and 95% nodal coverage (mm)

Direction from IPS	Median (range) distance from IPS (mm)	Margin for 90% nodal coverage (mm)	Margin for 95% nodal coverage (mm)
Cranial	20 (0-72)	44	**48**
Caudal	18 (1-60)	42	**50**

Abbreviations: IPS = inferior edge of pubic symphysis

delineation with respect to IPS to cover 95% of the nodes was at 48 and 50 mm, respectively (Table 1).

Relationship of the individual node with the surrounding structures

Out of the total 222 nodes analyzed, 10 nodes infiltrated into the skin, 22 nodes abutted the skin, and the remaining 200 nodes maintained a clear plane from the skin surface. There were 8 nodes abutting the surrounding muscles. There was no node infiltrating into any muscle radiologically. No node involved any surrounding bone. All nodes maintained a clear fat plane with the spermatic cord with none infiltrating the spermatic canal. There were 138 nodes lateral, 42 nodes postero-lateral, and 15 nodes antero-lateral to the spermatic cord in its entire course. There were 10 nodes superior and 17 nodes inferior to the entire extent of the spermatic cord. No nodes were seen medial to the spermatic cord.

Modification of the CTV margin to evolve contouring guidelines

The CTV margins grown around the femoral vessel obtained from this study in a reference radiation therapy planning CT scan of a patient with non-operated groin and a post-operative groin were reviewed by the investigators of this study and were modified from the surrounding structures as depicted in Figure 3A and B to evolve contouring guidelines for CTV delineation of the inguino-femoral region for penile cancer.

Clinical outcomes with proposed contouring guidelines

Between January 2018 and May 2020, 14 patients with operated penile SCC were treated with postoperative radiation therapy. The patient and treatment characteristics of each patient are summarized in Table 2. With a median follow up of 24 months (range, 5-31), 3 patients have died and 11 patients are alive without disease. Two of 3 patients died of disease. Of these, 1 patient developed distant metastasis without locoregional relapse, whereas the second patient developed both distant metastasis and regional in-field recurrence in the irradiated groin. The third patient had a noncancer-related death due to pre-existing chronic obstructive pulmonary disease, with no evidence of cancer at last follow-up. Grade 1 and grade 2 lymphedema was seen in 6 (42.8%) and 4 (28.5%) patients, respectively. Four (28.5%) patients had grade 1 skin toxicity. None of the patients developed grade 3 lymphedema or ≥ grade 2 skin toxicity (Table 2).

Discussion

This study analyzed the spatial distribution of radiologically positive inguinal nodes around femoral vessel in patients with biopsy-proven penile cancer to propose evidence-based guidelines for inguinal CTV delineation with both non-operated and post-operative groin. This is particularly important, as generalization of existing contouring guidelines for inguinal CTV delineation across the pelvic malignancies may be inappropriate owing to the rare occurrence of penile cancer. The results of the present study will aid in inguinal CTV delineation as the evidence of radiation therapy to the groin in penile cancer evolves.[5]

Three studies have previously evaluated the distribution of inguinal nodes in small cohorts of patients with heterogeneous primary pelvic malignancies. The study by Kim et al[8] reported optimal margins needed around the femoral vessels in 22 patients (55% had primary vulval cancer and the rest, 45%, included primary vaginal, anal, and cervical cancer with lower vaginal involvement) with a total of 52 positive inguinal nodes. Rao et al[9] identified 150 positive

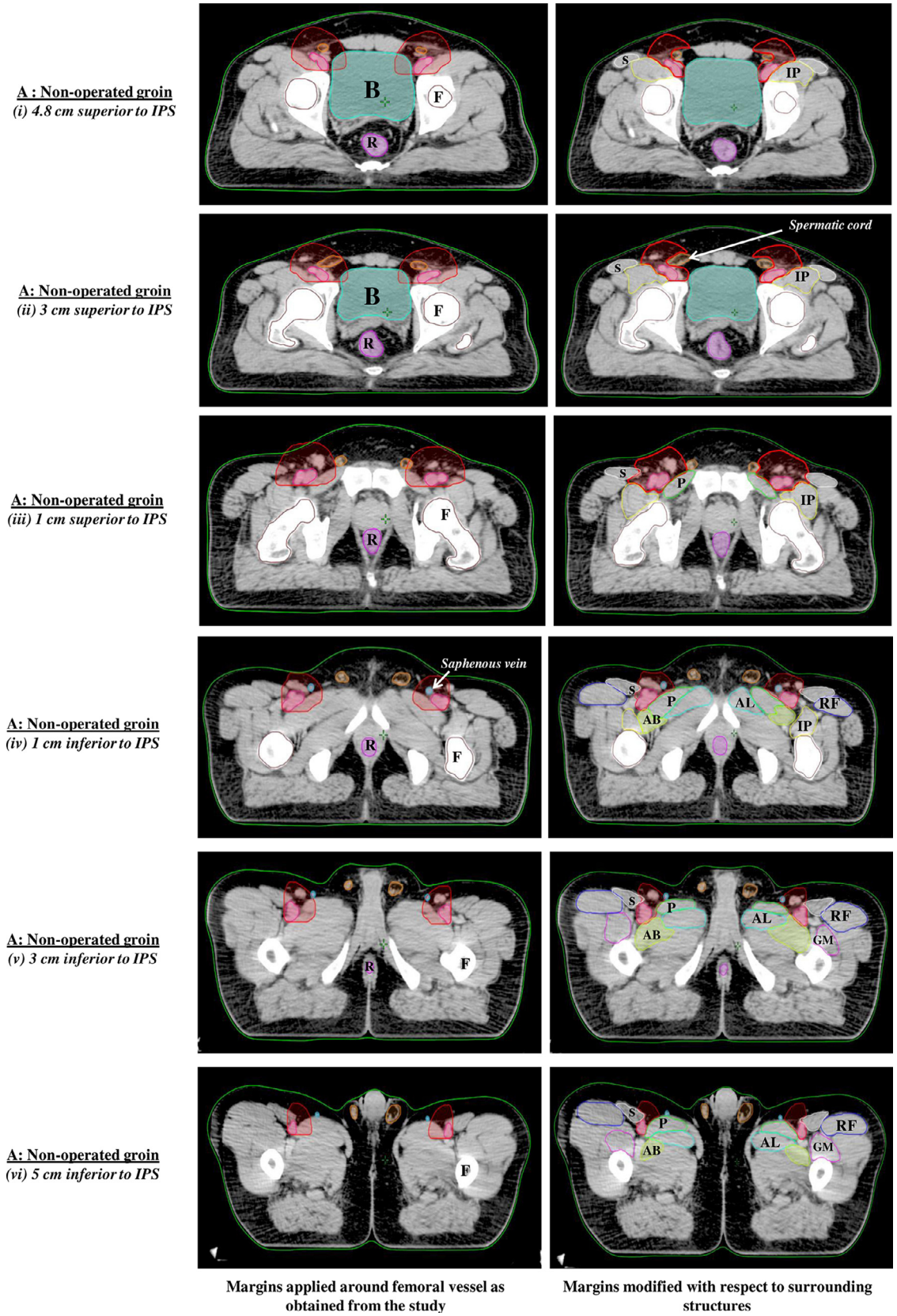


Fig. 3. Proposed contouring guidelines for inguinal clinical target volume (CTV) delineation (red) in penile cancer for 95% coverage of nodes in (A) non-operated groin and (B) post-operative groin. *Abbreviations:* AB = adductor brevis; AL = adductor longus muscle; B = bladder; F = femur; GM = gluteus medius; IP = ilio psoas; P = pectineus; R = rectum; RF = rectus femores; S = sartorius.

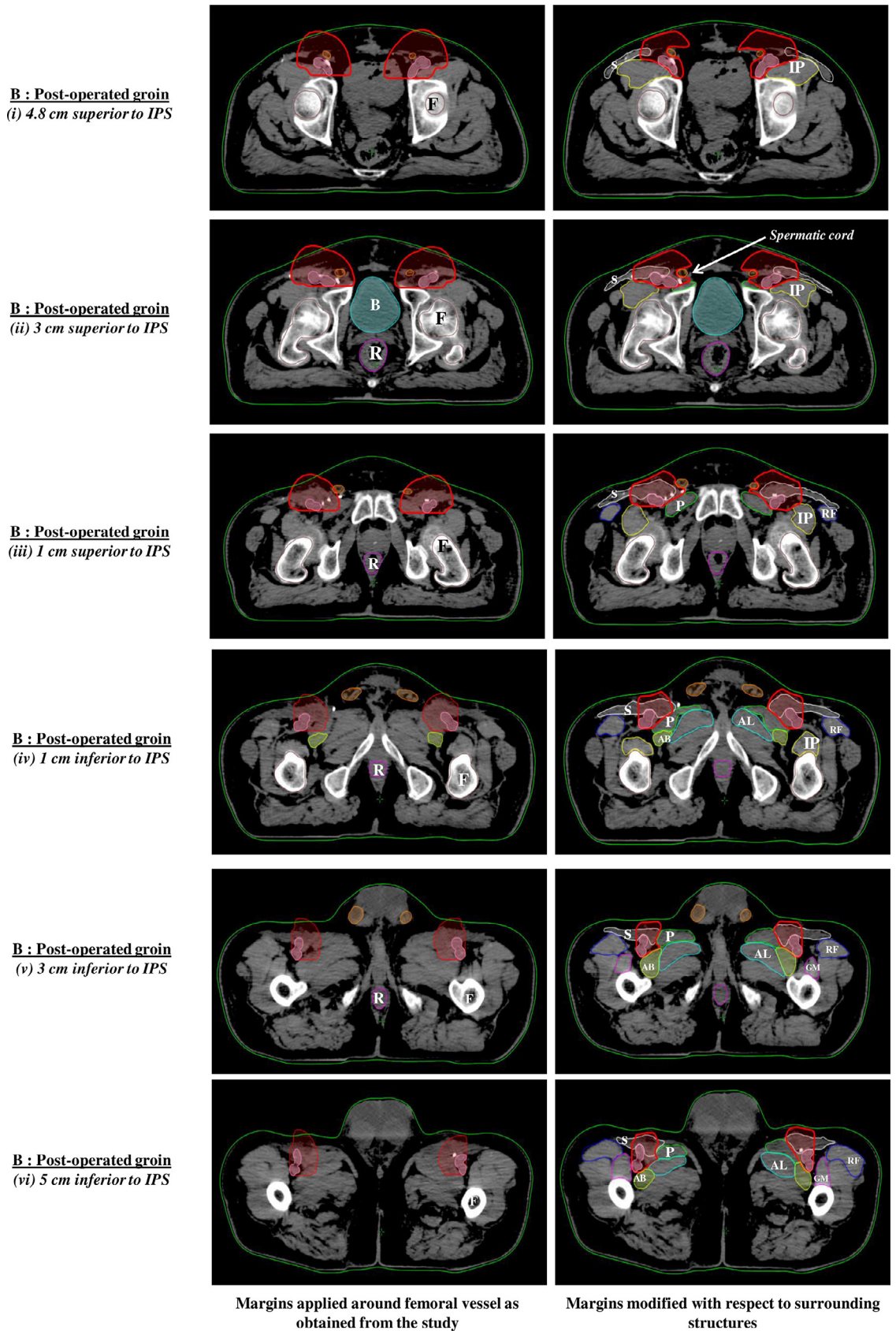


Fig. 3. Continued.

Table 2 Patient and treatment characteristics with clinical outcomes of prospectively treated patients with squamous cell carcinoma of penis with proposed inguinal CTV contouring guidelines

Patient number	Surgery	Stage	Adjuvant and concurrent chemotherapy	Adjuvant radiation therapy target volume	Technique (IMRT ± IGRT)	Duration of follow-up post- radiation therapy (months)	Status at last follow-up	Radiation therapy toxicity
1	Circumcision + bilateral radical GND + bilateral PLND	pT1 pN3	4* Adjuvant 5-FU + cisplatin; concurrent cisplatin	Bilateral groin + bilateral pelvic nodes	IMRT with EPID	31	Alive with NED	None
2	Partial penectomy + left radical GND + right modified GND + left PLND	pT2 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin + bilateral pelvic nodes	IMRT with EPID	30	Alive with NED	G2 lymphedema (CTCAE) G1 skin toxicity (RTOG)
3	Glans wide local excision with flap reconstruction + bilateral radical GND + right PLND	pT1 pN3	4* Adjuvant paclitaxel + cisplatin; Concurrent cisplatin	Bilateral groin + right pelvic nodes	IMRT with CBCT	29	Alive with NED	G1 lymphedema (CTCAE) G0 skin toxicity (RTOG)
4	Partial penectomy + bilateral radical GND + bilateral PLND	pT1 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cispatin	Bilateral groin + bilateral pelvic nodes	IMRT with CBCT	29	Alive with NED	G1 lymphedema (CTCAE) G0 skin toxicity (RTOG)
5	Total penectomy + bilateral radical GND + bilateral PLND	pT3 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin	IMRT with CBCT	26	Alive with NED	G2 lymphedema (CTCAE) G1 skin toxicity (RTOG)
6	Partial penectomy + right radical GND + left modified GND + right PLND	pT3 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin + right pelvic nodes	IMRT with CBCT	26	Alive with NED	G2 lymphedema (CTCAE) G0 skin toxicity (RTOG)
7	Circumcision + right radical GND + left modified GND + right PLND	pT1 pN3	No adjuvant; concurrent gemcitabine	Bilateral groin + bilateral pelvic nodes	IMRT (no IGRT)	24	Died due to other causes	None
8	Glansectomy + bilateral radical GND + bilateral PLND	pT2 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin + bilateral pelvic nodes	IMRT with EPID	24	Alive with NED	None
9	Partial penectomy + bilateral radical GND + bilateral PLND	pT3 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin + bilateral pelvic nodes	IMRT with EPID	15	Alive with NED	None
10	Total penectomy + bilateral radical GND + left PLND	pT3 N3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin + left pelvic nodes	IMRT with CBCT	11	Alive with NED	G1 lymphedema (CTCAE) G1 skin toxicity (RTOG)
11	Partial penectomy + bilateral radical GND + bilateral PLND	pT3 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin + bilateral pelvic nodes	IMRT with CBCT	10	Alive with NED	G1 lymphedema (CTCAE) G0 skin toxicity (RTOG)
12	Partial penectomy + right radical GND + left modified GND + right PLND	pT2 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin + right pelvic nodes	IMRT with CBCT	9	Alive with NED	G1 lymphedema (CTCAE) G0 skin toxicity (RTOG)
13	Partial penectomy + right radical GND + left modified GND + right PLND	pT2 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin + right pelvic nodes	IMRT with CBCT	7	Death due to disease (regional recurrence)	G1 lymphedema (CTCAE) G0 skin toxicity (RTOG)
14	Partial penectomy + bilateral radical GND + bilateral PLND	pT1 pN3	4* Adjuvant paclitaxel + cisplatin; concurrent cisplatin	Bilateral groin + bilateral pelvic nodes	IMRT with EPID	5	Death due to disease (LR controlled)	G2 lymphedema (CTCAE) G1 skin toxicity (RTOG)

Abbreviations: 5 FU = 5 fluoro-uracil; CBCT = cone beam computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CTV = clinical target volume; EPID = electronic portal imaging device; GND = groin nodal dissection; IGRT = image guided radiotherapy; IMRT = intensity modulated radiation therapy; LR = locoregional; NED = no evidence of disease; PLND = pelvic lymph node dissection; RTOG = Radiation Therapy Oncology Group.

* Cycles of chemotherapy

inguinal nodes in 50 patients (80% had primary cervical cancer with lower vaginal involvement and the rest, 18%, included primary rectum, bladder with urethral involvement, vulval, and anal cancer) and determined distribution of inguinal nodes around the vessels, margins needed around the vessels, and inferior extent of contouring in the inguinal region. Only 1 patient had primary penile cancer in this series. Recently, Garda et al[10] characterized the spatial distribution of inguinal nodes in 40 patients with primary anal cancer and proposed guidelines for elective inguinal node CTV delineation. The present study is unique, as it reports the distribution of inguinal lymph nodes exclusively in patients with penile cancer.

The location of each involved node in the present study was determined with respect to a bony reference point, that is, the IPS. The IPS denotes a point on the inferior-most extent of the pubic symphysis and is identified on an axial CT scan slice before it continues as inferior pubic rami. IPS was chosen as a reference point as it is easily identifiable and remains constant in a patient with both non-operated and post-operative groin. A unique approach was devised in this study where the location of nodes was divided into 2 parts: nodes at and superior to the level of IPS (supra-IPS) and nodes inferior to the level of IPS (infra-IPS). This was done to account for the funnel-shaped distribution of nodes around the femoral vessels with a wider distribution of nodes superior to IPS near the saphenofemoral junction. This allows determining and reporting differential margins around the femoral vessels along its length. This approach was not undertaken by the previously published studies, and a uniform circumferential margin in different directions around the femoral vessels has been recommended. Of the total 222 nodes evaluated in the present study, 70% (155) were located superior (147 nodes) and at the level (8 nodes) of IPS. The remaining 30% (67) were located inferior to IPS. With respect to femoral vessels, 99% (220) of the nodes were located anterior to the femoral vessels, 81% (181) were located antero-medially, and 18% (39) were located antero-laterally. A majority (95%) of the antero-laterally located nodes were superior to IPS. No nodes were present antero-laterally to the femoral vessel inferior to the IPS.

If the location of inguinal nodes is represented on a clock face with the right femoral artery as the center point, then the nodes in the present study were located from 10 to 3 o'clock. This is different from the study by Kim et al (mainly vulval cancers) and Garda et al (anal canal), where nodes were also present lateral and posterior to the vessel and had a 9 to 6 o'clock and 10 to 4 o'clock distribution, respectively. Table 3 shows the comparison of the recommended margins in the previous studies with the present study where the recommended margin around the femoral vessels to cover 95% of the nodes for the supra-IPS region in anterior, medial, and lateral directions is 29, 23, and 21 mm, respectively, and for the infra-IPS region in anterior and medial directions is 21 and 23 mm, respectively. No margin is required posteriorly in supra-IPS and posteriorly and laterally in the infra-IPS region in relation to femoral vessels. The cranial and caudal extent of inguinal CTV in the present study is reported to be at 48 and 50 mm, respectively, with respect to IPS to cover 95% of the nodes. Rao et al and Garda et al reported cranial extent of inguinal CTV delineation to be at the level where external iliac artery leaves the bony pelvis and becomes femoral artery, unlike the present study where the cranial extent is based on evidence of location of each involved node with respect to a bony reference point (IPS).

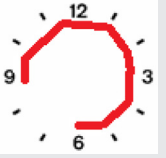
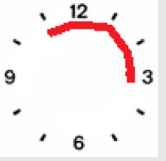
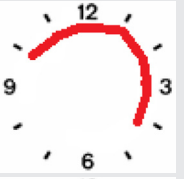
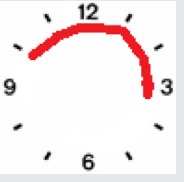
A final summary of step-by-step guide to delineate inguinal CTV is depicted in Table 4. The CTV margins obtained from the present study were grown around the femoral vessels in a reference radiation therapy planning CT scan of a patient with non-operated groin and a post-operative groin and were modified from the surrounding structures, as depicted in Figure 3A and B. For all patients, the CTV should be first edited from the skin in all the areas where it extends outside the body contour. It is also edited from the spermatic cord, bone, and bladder. For non-operated groin alone, the CTV should be edited from the surrounding muscle. The anatomic boundaries are laterally, the medial border of the sartorius and the iliopsoas muscle; medially, pectineus, adductor longus, and the adductor brevis muscle; posteriorly, iliopsoas and pectineus muscles. The vascular spaces at risk should be included in the CTV. Any other abnormalities, including grossly enlarged or suspicious nodes felt to be at risk that may harbor microscopic disease, should be included within the CTV based on treating clinician's judgment and imaging findings.

For post-operative groin alone, the CTV should be edited from the surrounding muscle. The anatomic boundaries are laterally, iliopsoas muscle; medially, pectineus, adductor longus, and the adductor brevis muscle; posteriorly, iliopsoas and pectineus muscles. Post groin dissection, sartorius muscle is transposed in the form of a twist rotation flap to form the roof of the exposed femoral vessels, and this corresponds to a high-risk region, especially as these patients are likely to have extranodal extension. Therefore, it is recommended not to edit the part of the CTV extending into the transposed sartorius muscle. This is also similar to the analogous situation while delineating postoperative nodal CTV in node positive head neck cancers where the muscle segment overlying the high-risk areas are included in the CTV.[13] However, the CTV should not be modified or extended beyond the recommended margins to include the entire transverse extent of the sartorius muscle to prevent excessive normal tissue toxicity.

The surgical and vascular clips placed in the operative bed do not necessarily indicate the extent of tumor bed or site of pathologically positive node. Therefore, it is recommended that all clips should not necessarily be included in the CTV, only the ones that are within the applied CTV margins should be included. However, the inclusion of the clip/s outside the generated volumes is at the clinician's discretion based on the operative notes.

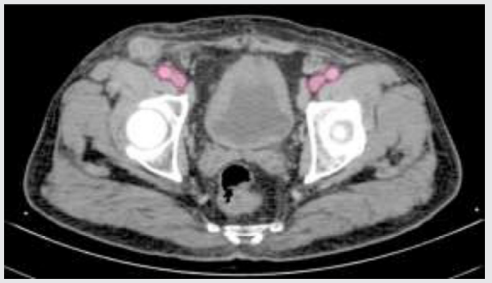
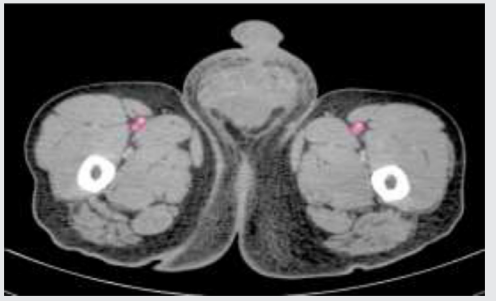
A lymphocele is a cyst filled with clear lymph fluid with no inflammatory or granulomatous reaction within it. It is self-limiting and usually self-heals without treatment.[14]

Table 3 Comparison of margins (mm) recommended for 95% inguinal nodal coverage around femoral vessels as per primary pelvic malignancy

Study	Anterior	Posterior	Medial	Lateral	Cranial	Caudal	O'clock distribution of nodes around femoral vessels
Kim et al[8](vulval cancer)	≥20 mm	≥20 mm	≥20 mm	≥20 mm	Not reported	Not reported	
Rao et al[9](cervical cancer with lower vaginal involvement)	25 mm	0 mm	15 mm	0 mm	At the level where external iliac artery leaves the bony pelvis and becomes femoral artery	2 cm below the lesser trochanter	
Garda et al[10](anal cancer)	30 mm	0 mm	26 mm	0 mm	At the level where external iliac artery leaves the bony pelvis and becomes femoral artery	14 mm caudal to IPS	
Present study (penile cancer)	SIPS: 29 mm IIPS: 21 mm	SIPS: 0 mm IIPS: 0 mm	SIPS: 23 mm IIPS: 23 mm	SIPS: 21 mm IIPS: 0 mm	48 mm cranial to IPS	50 mm caudal to IPS	

Abbreviations: IIPS = infra-IPS; IPS = inferior edge of pubic symphysis; SIPS = supra-IPS.

Table 4 Step-by-step guide to delineate inguinal CTV in penile cancer

Step 1: Contouring femoral vessels Identify IPS in 3D. Contour femoral vessels (artery + vein) in supra- and IIPS regions separately (craniocaudal length of vessels as per 95% nodal coverage in Table 1).				
Region	SIPS region		IIPS region	
Structure	SIPS_Rt_femoral_vessel	SIPS_Lt_femoral_vessel	IIPS_Rt_femoral_vessel	IIPS_Lt_femoral_vessel
	Cranially 48 mm superior from IPS		Caudally 50 mm inferior from IPS	
				
Step 2: Delineating normal structures Bladder, rectum, femoral heads, spermatic cords				
Step 3: Generation of inguinal CTV Using 95% margins in Table 1, expand asymmetrically around the femoral vessels to generate separate CTVs in SIPS and IIPS regions (Fig. 3A,B)				
Region	SIPS region		IIPS region	
Structure	SIPS_Rt_inguinal_CTV	SIPS_Lt_inguinal_CTV	IIPS_Rt_inguinal_CTV	IIPS_Lt_inguinal_CTV
Step 4: Modification of inguinal CTV margins Inguinal CTV is edited from normal structures, muscles, and bones (Fig. 3A,B)				
Step 5: Boolean operations to generate final right and left inguinal CTV				
Structure	Rt_inguinal_CTV =	SIPS_Rt_inguinal_CTV + IIPS_Rt_inguinal_CTV	Lt_inguinal_CTV =	SIPS_Lt_inguinal_CTV + IIPS_Lt_inguinal_CTV

Abbreviations: 3D = 3-dimentional; CTV = clinical target volume; IIPS = infra-IPS; IPS = inferior edge of pubic symphysis; SIPS = supra-IPS.

Therefore, the applied CTV margins, if they include a volume of lymphocele, should not be edited, modified, or extended to include the entire lymphocele. However, the inclusion of the entire lymphocele may be indicated outside the generated CTV if the lymphocele is present at the site of the pathologically involved lymph node, especially with extranodal extension. It is advisable to look at the preoperative imaging to correlate the exact site of the involved node.

All relevant surgical scars should be marked with radiopaque wires and visible on the planning CT scan. Extending the CTV beyond the recommended margins to include the entire surgical scar is at the clinician's discretion, although generally not recommended. In our prospective cohort that was used for clinical validation of the recommended margins, none developed marginal or out-field surgical scar recurrence. In the case of clinic-radiological evidence of skin or subcutaneous tissue infiltration, a 3- to 5-mm tissue equivalent bolus may be placed over the region to avoid underdosing. Any other abnormalities felt to be at risk that may harbor microscopic disease should be included within the CTV based on the treating clinician's judgment, intraoperative observations, and histopathology report.

The routine inclusion of prepubic fat as a part of CTV for all patients, as has been suggested by Korzeniowski and Crook,[15] is debatable. Prepubic fat has been considered as an aberrant site for location of sentinel lymph nodes, and it is rare to find a lymph node in this region, especially with modern imaging.[16,17] Also, prepubic fat is usually not surgically violated except in patients who have extensive primary disease reaching up to the base of the penile shaft needing a radical penectomy. Therefore, it is not recommended to prophylactically include prepubic fat routinely, especially as it can cause excessive dose spillage to midline normal structures.

Although this study is the first to exclusively report and clinically validate the inguinal CTV margins in penile cancer, certain limitations are acknowledged. First, the current study is limited by the number of patients included given the relative rarity of penile cancer. Second, we relied primarily on radiological diagnosis of lymph node involvement, and it is possible that some lymph nodes analyzed in our study were false positives or false negatives, and therefore we involved a diagnostic radiologist trained in interpreting pelvic scans as per mentioned radiological criteria for nodal positivity. Also, we made 2 assumptions while marking the radiological center of the lymph node in this study. The first was that the center of the positive node is the center of the normal node, and second, that the positive node enlarges symmetrically, which may or may not be correct. Also, the positive node may enlarge asymmetrically, and therefore the true microscopic extent of the disease may actually be smaller or larger than our suggested boundaries. However, on prospective clinical validation of the proposed contouring guidelines presented in this study, none of the patients developed marginal or out-of-the-field recurrences, with only 1 patient developing infield recurrence in the groin along with distant metastasis, possibly owing to bad disease. The current study did not assess the effect of leg positioning on recommended margins, as the guidelines were made from scans in the supine position. We chose a unique bony reference point, that is, the IPS, which is present in the midline, a clearly identifiable part of the pelvic bone that is relatively stable with respect to the groin. There might be a minor variation with a change in leg positioning, that is, supine versus frog-leg position. However, this variation may be limited to the cranio-caudal directions, and the margins recommended for the same in the current study should be adequate to cover the supero-inferior extent of the inguinal nodal region. Finally, the anatomic relationships can be affected by the body mass, and hence there can be variation in anterior distribution of nodes in relation to the femoral vessel depth with variation of body mass index.[6] However, in this study, due to inadequate body mass index information of the study cohort, this variation could not be done. Instead we measured femoral vessel depth (FVD) at the level of IPS for all patients (n = 33). The median FVD was 33 mm (interquartile range, 3.08-3.8), which is similar to the FVD (35 mm) of the representative patient/s illustrated in the contouring atlas supporting that the recommended margins are adequate for complete inguinal nodal coverage. However, there is a need for modifying the CTV margins using clinical judgment in patients who may be outliers in terms of size/anatomy to ensure adequate coverage of deep as well as superficial inguinal nodal regions.

Conclusions

This study analyzed patterns of distribution of inguinal nodes to propose guidelines for inguinal CTV delineation exclusively in penile cancer. The proposed guidelines were validated prospectively in a small cohort of patients and found to be implementable and safe. Larger validation is needed to further refine and adopt them in clinical practice.

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