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Impact of radiation therapy on perineal urethrostomy for penile cancer

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ABSTRACT

Objective: A lack of demonstrated clinical benefit precludes radiotherapy (RT) from being recommended for pN1/pN2 penile cancer (PeCa) lesions; but it may be recommended in case of extranodal (pN3) disease or for positive resection margins. Perineal urethrostomy (PU) is a technique of urinary diversion in patients with PeCa requiring total or subtotal penectomy as primary therapy. Prior studies suggest PU failure rates of up to 30%, without specific mention of the potential role of RT. When RT is delivered for PeCa it is usually to the pre-pubic fat, groin and lateral pelvis, and not to the region of the PU. Here we describe the role of perioperative RT in a large, multi-institutional registry of PU for PeCa.

Methods: In our cohort, 299 patients from seven international, high-volume centers in Belgium, Brazil, China, Netherlands, United Kingdom and the United States underwent PU as urinary diversion for PeCa between 2000 and 2020. Demographic and clinicopathologic characteristics were reviewed.

Results: Median patient age was 67 years and median follow-up was 19 months. Seven patients (2.3%) received pre-operative RT; six of them with chemotherapy. 37 received RT post-operatively, 21 (57%) with chemotherapy. Stenosis of the PU occurred in 35 (12%) of the total population. The majority of these patients (74%) required surgical revision at a median of 6.1 months post-operatively. RT delivery was neither significantly related to PU stenosis ($p = 0.16$) or to subsequent revision ($p = 0.75$).

Conclusion: Receipt of RT was not significantly associated with increased stenosis risk in PeCa patients who underwent PU.

Introduction

Squamous cell carcinoma of the penis (PeCa) is rare but may be associated both with a potential for bulky local and regional spread and aggressive metastases [1]. While brachytherapy has been described for small volume local primary disease [2], standard therapy for PeCa is usually surgical. Total or partial penectomy techniques are favored for bulky primary lesions, with standard inguinal lymph node dissections (ILND) as indicated. Few data support the role of radiation therapy (RT) in penile cancer; in fact, adjuvant RT is not recommended following resection of pN1 or pN2 disease [3]. We have documented a potential benefit of post-operative RT for pN3 disease, by virtue of either ECE [4] or presence of pelvic nodal disease [5]. The ongoing International Penile Advanced Cancer Trial (InPACT) trial [6] is an important step forward in adjuvant management of PeCa. InPACT is co-sponsored by the Institute of Cancer Research (UK/EU) and the US National Cancer Institute and

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Table 1
Clinical characteristics.

Parameter	n (%)
Age, y (med)	67 (IQR: 58–74)
Follow-up, m (med)	19 (IQR: 7.2–57)
pT stage	
pT1	46 (15)
pT2	108 (36)
pT3/4	116 (44)
pTx	14 (5)
pN stage	
pN0	53 (18)
pN1	41 (14)
pN2	36 (12)
pN3	39 (13)
pNx	130 (43)
Positive resection margin	17 (5.7)
Neoadjuvant treatment	
Chemotherapy	15 (5.0)
Radiation	1 (0.33)
Chemoradiation	6 (2.0)
Adjuvant treatment	
Chemotherapy	12 (4.0)
Radiation	16 (4.4)
Chemoradiation	21 (7.0)
Unknown	4 (1.3)

Y = years; m = months; med = median; n = number; IQR: Interquartile range; pT = pathological T; pN = pathological N.

Table 2
Number of stenosis and surgical revisions of PUs after adjuvant (chemo) radiotherapy.

	PU stenosis			Surgical revision PU stenosis		
	Yes	No		Yes	No	
Adjuvant (chemo) radiotherapy			p = 0.16*			p = 0.75*
Yes, n (%)	7 (19)	30 (81)		2 (5)	35 (95)	
No, n (%)	27 (10)	231 (90)		23 (9)	235 (91)	

PU = perineal urethrostomy; * Fishers exact test.

has accrued ~25% of the programmed patient goal.

The preferred technique for urinary diversion following total penectomy often is perineal urethrostomy (PU). Most PU data have been described in the context of benign urethral conditions [7], because of the rarity of PeCa. Following PU, revision rates as high as 30% have been reported [8]. We recently described a large multinational report of the use of PU in PeCa, with attention to acute complications and revision and stricture rates [9]. The clinical diagnosis of urethral stenosis is a hindrance of urinary stream often, ischemic/fibrotic in etiology, at the site of the prior perineal skin and urethral anastomosis causing symptoms (typically obstructive) or resulting in clinical sequelae (e.g. urinary tract infection, acute urinary retention).We theorize the role of RT is most critical in the process of stenosis, and less crucial in revision, since many other factors might contribute to the surgeons' decision for revision: including patient choice, performance status and comorbid conditions. The goal of this manuscript is to expand on the role of RT with PU, with attention to its role in stenosis and recommended techniques.

Material and methods

Our study involved a retrospective review of 304 medical records of consecutive penectomy patients treated between June 2000 and February 2020 for non-metastatic PeCa across seven international centres in Brazil, China, Europe, United Kingdom and the United States. After approval from the appropriate Institutional Review Boards, analyzed variables included age, pathologic tumor and node staging (7th Ed., American Joint Committee on Cancer), length of stay, primary tumour surgery, and adjuvant therapy. 30-day complications were collated for 299 patients with complete postoperative data, as was time to PU stenosis. Complications were quantified using the Clavien–Dindo (CD) classification system [10]. Fishers exact test was used for comparison. A p-value of <0.05 was deemed significant.

Results

Standard institutional FU for penile cancer was mostly 5 years, although no time limit was used for stenosis in this study. Median FU with exclusion of deceased patients was 44 months (IQR 15–61) months. Positive resection margins were rare and noted in 5.7% of all patients (n = 17). Neoadjuvant and adjuvant therapy data are in Table 1. The former was provided in 7.3% and the latter in 16% of patients. 30-day postoperative complications occurred in 19% of patients (n = 58); these generally were wound infections (11%) or dehiscence (4.0%). 46 complications were minor (CD Grade I/II). The rest were major complications, of which 10 were CD grade III [10]. Due to cardiopulmonary complications 2 patients were admitted to the ICU of which one died (CD grade IV and V).

Stenosis frequency was 12% (35/299 patients). Only two cases of stenosis were observed more than 2 years post-operatively, at 3.4 and 4.3 years after surgery. The location of stenosis was at the neo-meatus in almost all (90%) cases. No patient who developed stenosis had a positive surgical margin or received neoadjuvant therapy [10].

Of the 299 patients, 49 (16%) received documented adjuvant therapy and 37 received adjuvant (chemo)radiotherapy. Seven of these 37 patients (19%) developed stenosis, of which only 2 underwent surgical revision. However, 28 of the 246 patients (11%) without any adjuvant therapy developed stenosis, of which 23 underwent surgical revision. Neither the rates of stenosis (p = 0.16) nor the subsequent rates of revision (p = 0.75) were statistically different (Table 2).

Discussion

Delivery of RT in conjunction with PU may be necessary from the perspective of local cancer control; in such cases the potential benefits outweigh the risks of developing a stenosis of the PU. Given the fragility of the PU and the known role of RT to precipitate tissue fibrosis, it might be expected that RT, especially given adjuvantly, would contribute to PU stenosis and potential revision. In our prior analysis [9] a cox regression analysis was performed for surgically revised stenosis because the exact dates the conservatively treated stenosis were diagnosed are unknown. There are numerically more episodes of stenosis after adjuvant (chemo) radiotherapy (19% vs 10%) but a lower frequency of surgical revision afterwards (5% vs 9%) (Table 2); both of these differences are non-significant. A possible explanation for this might be that urologic surgeons might tend to avoid surgery in patients who had received previous radiotherapy.

There are several reasons why RT may not contribute to stenosis in this analysis. First, as in any retrospective analysis of a rare process, it may simply be that our data did not include enough RT cases to document an association. Secondly, adjuvant therapies are infrequently used as a rule in PeCa: only in about one of seven cases in our review. This is because the limited data reveals only a potential role for RT in selected primary lesions [2] and in pN3 patients [4,5].

The final reason is that standard RT fields for PeCa does not include the path of the PU unless there is a positive penile margin, and this is also a rare occurrence after total penectomy (fewer than 6% of our patients). As an example, compare the two clinical cases in Fig. 1. In Fig. 1a patient with cN2 disease after total penectomy is being treated pre-operatively on the InPACT trial [6]. The pre-operative dose is 45 Gy. The field extends caudally to properly include involved inguinofemoral lymph

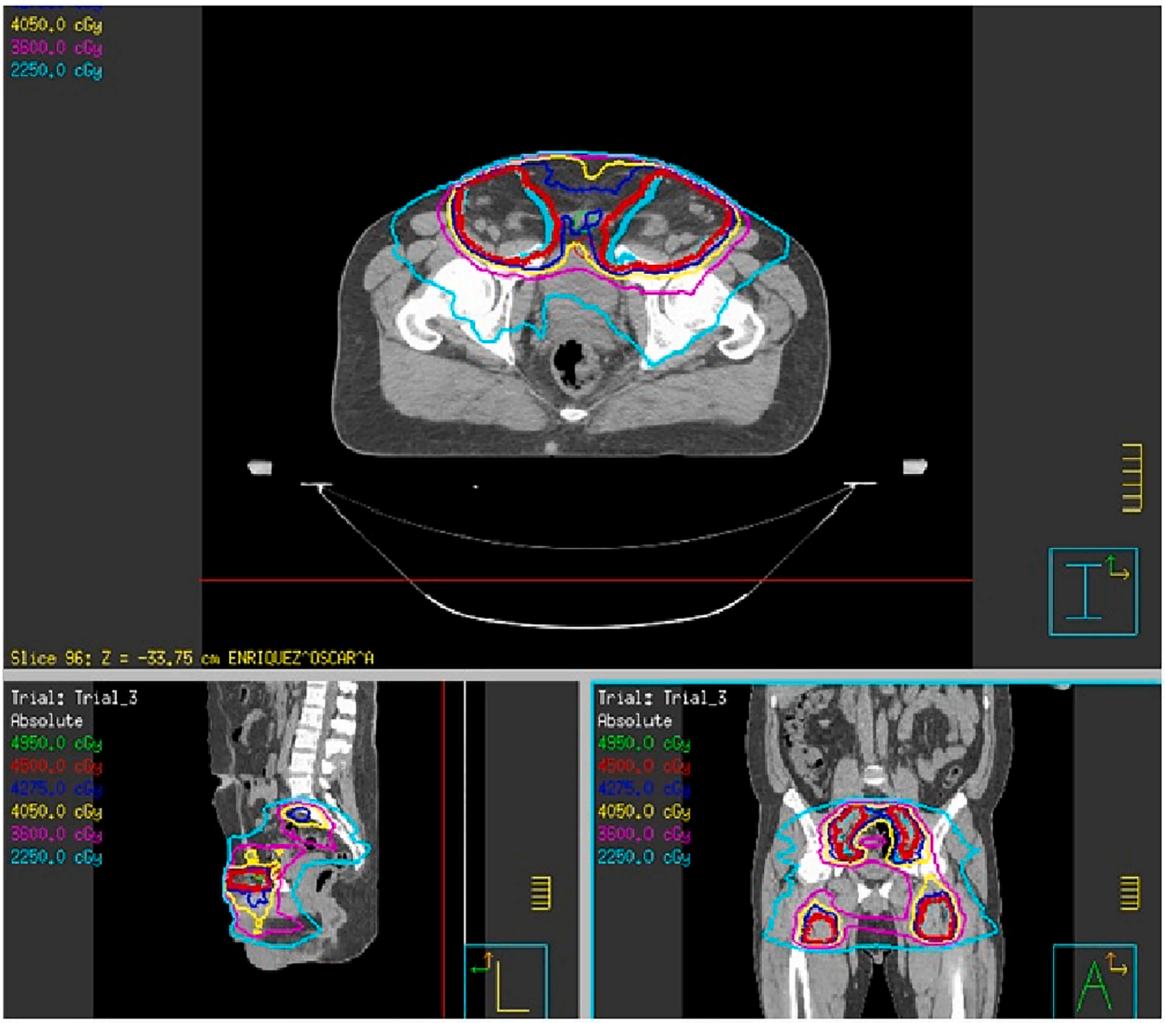

Fig. 1a. Axial slice of a dosimetry plan for cN2 penile cancer patient being treated pre-operatively on InPACT trial [6] after total penectomy. Red isodose line is 45 Gy in 25 fractions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

nodes, but the central inferior pelvis is covered only by the 50% isodose line. Fig. 1b tells an entirely different story. At the time of total penectomy, positive margins were noted on the pubis and urethra with likely local extension of gross disease into the inferior right pubic bone. With pT4cN0 PeCa, he also had T1c prostate cancer (Gleason grade group 1) diagnosed 6 years earlier and untreated. He was not an InPACT candidate. In this case, three volumes of different potential RT dose were considered: gross disease in prostate and inferior right pubis, microscopic disease about pubis and PU, and potential subclinical disease in the clinically negative groins bilaterally. We have previously published that standard 50 Gy doses for microscopic PeCa are clinically insufficient and not supported by genomic analysis of PeCa primary [11] and nodal specimens [12]. Thus the prescribed doses were 70.2 Gy in 26 fractions to the prostate and right inferior pubis, 62.4 Gy in 26 fractions to pubic tumor bed and length of PU [EQ2D of 64.5 Gy for α/β of 10]), and 52 Gy in 26 fractions to the undissected bilateral groins and prepubic fat. Because of persistent bladder spasm during RT, he was treated with a catheter in place.

Our analysis describes complication rates after PU and the minor role of RT, admittedly with significant limitations due to its retrospective nature, lack of RT and chemotherapy information, and global, multi-institution scope. Some may consider that the lack of substantial information on doses and fields of RT affects the robustness of the results, and that solid conclusions extracted from the study are doubtful. Practically, one might expect that varying techniques from 2D to IMRT with image guidance would have been used, based on the technology available at the time. Varied photon energies and even electron therapy may have been used by the reporting centers. However this manuscript is the first investigating the topic, and we consider the conclusion herein to be well supported despite the acknowledged drawbacks.

Undoubtedly, PeCa has enormous impact on numerous quality of life areas [13–16] for patients. Organ preservation techniques certainly exist for selected patients, but radical surgery remains the best choice for many primary lesions, and for the involved groin in all cases [17]. In such cases, PU is a reliable and effective mechanism of urinary diversion. Regardless of whether or not adjuvant therapy is provided, surgical revision of PU for stenosis is required in about a tenth of cases within the first two years of treatment. In this review, receipt of RT was not associated with increased stenosis risk in PeCa patients who underwent PU.

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.

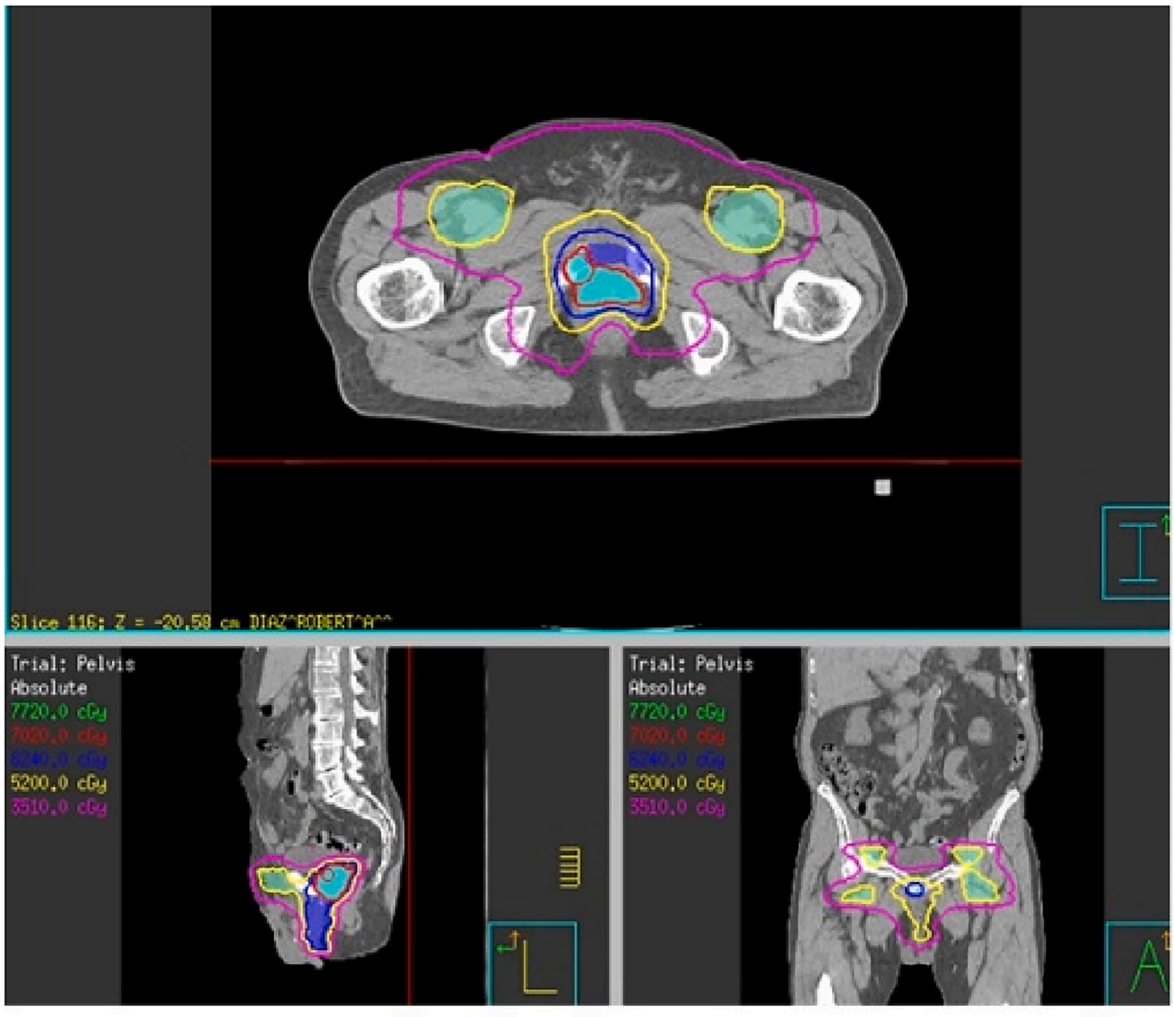

Fig. 1b. Axial, sagittal and coronal slices of a dosimetry plan for pT4cN0 penile and T1c prostate cancer patient being treated for positive bone and urethral margins after total penectomy with perineal urethrostomy. Red isodose line is 70.2 Gy in 26 fractions (gross disease in prostate and right pubis). Blue isodose line is 62.4 Gy in 26 fractions (microscopic disease [EQ2D of 64.5 Gy for a/b of 10] at pubis and urethra). Yellow isodose line is 52 Gy in 26 fractions (undissected cN0 groins and prepubic fat). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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