# Role of Penile Doppler US in the Preoperative Assessment of Penile Squamous Cell Carcinoma Patients: Results From a Large Prospective Multicenter European Study

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**OBJECTIVE** To determine the role of penile Doppler ultrasound (PDU) compared with magnetic resonance imaging (MRI) in preoperative diagnostic evaluation of patients with penile squamous cell carcinoma.

**MATERIALS AND METHODS** A prospective analysis on patients presenting with clinical diagnosis of penile squamous cell carcinoma from 6 different European hospitals between 2012 and 2014 was carried out. Each patient who had planned an organ sparing approach underwent an MRI and PDU both with an artificial erection with prostaglandin E 1. Age, evidence of MRI or PDU corpora cavernosa infiltration, frozen section examination report, definitive pathological report, and surgical approach used per patient were recorded. Accuracy, precision, negative predictive value, sensitivity, and specificity were calculated. Outcomes were statistically evaluated.

**RESULTS** Two hundred patients were enrolled in the study. The mean age of the patients was 67.35 ± 15.45 (range 51-82). All of the patients were treated surgically. Of the 200 patients, 135 (67.5%) underwent a corpora sparing approach, whereas 65 had a partial penectomy because of the frozen section outcome. About corpora cavernosa infiltration, the definitive outcome confirmed the frozen section examination. PDU vs MRI accuracy was 96.5% vs 90.5%; precision was 92.6% vs 96%; sensitivity was 96.9% vs 73.8%, specificity was 96.2% vs 98.5%. Despite sensitivity ($P$ <.05) no statistical evidence was found between ultrasound and MRI.

**CONCLUSION** PDU has a statistical similar outcome on detecting infiltration of corpora cavernosa and could be used as a less expensive tool to drive surgical strategy in patient with a diagnosis of penile squamous cell carcinoma. UROLOGY 90: 131–135, 2016. © 2016 Elsevier Inc.

Penile carcinoma is mostly a squamous cell carcinoma (SCC). Penile carcinoma usually originates from the epithelium of the inner prepuce or the glans and occurs in several histological subtypes.[1] In Western countries, primary penile cancer is uncommon, with an incidence of <1.00 per 100,000 males in Europe and the United States.[2] In European countries, the overall incidence has been stable from the 1980s until today.[3] Recently, an increased incidence has been reported from Denmark[4] and the UK. A longitudinal study from the UK has confirmed a 21% increase in incidence over the period 1979-2009.[5] The incidence of penile cancer increases with age,[3] with an age peak during the sixth decade of life. However, the disease does occur in younger men.[6] Phimosis is strongly associated with the development of invasive penile cancer (odds ratio: 11.4; 95% confidence interval: 5.0-25.9), probably due to associated chronic infection because smegma is not a carcinogen.[7] Penile carcinoma is often a clinically obvious lesion but can be hidden under a phimosis. Physical examination of a patient with penile

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cancer should include palpation of the penis with a view to examining the extent of local invasion.[1] The aims of the treatment of the primary penile cancer lesion are complete tumour removal with as much organ preservation as possible and radicality of the treatment should not be compromised. A local recurrence in itself has little influence on long-term survival so that organ preservation strategies are justified.[8] If organ preservation is planned and preoperative decisions are needed, magnetic resonance imaging (MRI) in combination with an artificial erection with prostaglandin E 1 can be used to exclude tumour invasion of the corpora cavernosa (CC).[9,10] Some studies have started to underline the role of ultrasound that can give information about infiltration of the CC.[11,12] In this prospective study, we wanted to evaluate the role of penile Doppler ultrasound (PDU) with CC prostaglandin E 1 injection compared with the one of MRI in preoperative assessment of penile SCC.

## MATERIALS AND METHODS

A prospective analysis on patients presenting with a first clinical diagnosis of penile SCC from 6 different European Hospitals between January 2012 and December 2014 was carried out. The study was approved by our local Ethical Committee. All tumours emerged from the glans. Primary tumours were staged according to the 2009 TNM system.[13] Patients with no palpable infiltration of the glans and eligible for conservative treatments[14,15] and patients with a previous diagnosis of SCC who received any treatment for this reason were excluded from this study. Written informed consent was obtained from each patient. All patients as a preoperative assessment underwent a PDU evaluation and MRI, both with an artificial erection with intracavernous 10 μm of prostaglandin E 1. The PDU was performed by a senior consultant urologist with a background expertise on penile ultrasound (the same for each participating center) using a MyLAb 75 HD (Esaote, Firenze, Italy) with a 10 MHz linear-array small-parts transducer. We considered a senior consultant urologist with a background expertise on penile ultrasound or a consultant urologist with at least 5 years of experience with a completion of an accredited residency program or fellowship or postgraduate training (other than in urology) that includes structured training in diagnostic urologic ultrasound, under the supervision of a qualified physician(s), during which the trainee will have evidence of being involved with the performance, evaluation, interpretation, and reporting of at least 100 diagnostic urologic ultrasound examinations. Each of the 6 centers met these criteria. The tumour was identified by the presence of hypoechoic lesions on the ultrasonograms that were not consistent with normal penile anatomy.[16] The PDU report was hidden and reconsidered for data analyzing after the surgical procedure and the definitive pathological outcome. MRI was performed using a 1.5 T Magnetom Scanner (Siemens GmbH, Germany) with a small surface coil. In MRI, a gel pad was used to avoid artefacts, and a urethral catheter was introduced for identification. All the MRI scans were reviewed by a senior radiologist with uro-andrological MRI expertise (1 in each hospital) and with no previous knowledge of the clinical data. We considered a senior radiologist with uro-andrological MRI expertise or a consultant radiologist with at least 5 years of experience in uro-andro-oncological field, who works in a tertiary referral hospital for uro-oncology. Each of the 6 centers met these criteria. MR images were obtained in the axial plane using T1-weighted spin echo (T1-SE) and T2-weighted turbo-spin echo (T2-TSE) sequences. Sagittal images were acquired using a short tau inversion recovery sequence and T1-SE sequences, before and after administering an intravenous contrast agent (gadolinium based). Tumour identification was mainly based on the presence of lesions with low signal intensity relative to the corporal bodies on the T1- or the T2-weighted images including diffusion imaging.[16] Invasion by tumour of the corpus spongiosum, CC, and urethra was assessed. Infiltration depth was measured from the surface of the nearby uninvolved epithelium to the area of maximum invasive growth. If there was total destruction of the glans by tumour, the infiltration depth was measured from the top of the tumour to the area of maximum invasive growth. Once the MRI was performed, surgical procedure was scheduled. Treatment consisted of glansectomy[17] or partial penectomy[18] if an infiltration of the CC and urethra was assessed during the frozen section examination (FSE)[1] which confirmed or not the MRI report about corpora infiltration. In each case, a tumour-free margin of 5 mm has been considered safe.[17,19] The results of the PDU and MRI were compared with the FSE and the definitive histopathological outcome of the specimen was obtained at surgery. Paraffin-embedded haematoxylin and eosin-stained slides were used. Tumour size was then determined, and the relation to the various anatomical structures of the penis was assessed. Infiltration depth was measured from the intact basal membrane at the edge of the tumour to the deepest tumour extension. If there was total destruction of the glans by tumour, the infiltration depth was measured from the top of the tumour to the deepest tumour extension. Patients' age, evidence of MRI or PDU CC infiltration, FSE report, definitive pathological report, and surgical approach were recorded. Accuracy, precision, negative predictive value, sensitivity, and specificity were calculated. Outcomes were statistically evaluated.

## RESULTS

A total of 200 patients were enrolled in the study. Table 1 summarizes patient's characteristics. The mean age of the patients was 67.35 ± 15.45 years (range 51-82 years). All of the patients were treated surgically as they were all classified as clinical T2. Tumour size was 31.2 ± 12.11 mm (range 12-61 mm) at the definitive pathological outcome. Of the 200 patients, 135 (67.5%) underwent glansectomy with a CC sparing approach, whereas 65 (32.5%) had a partial penectomy because the FSE outcome revealed a CC infiltration. Ten patients (5%) had also a urethral infiltration, so they were classified as a pT3. Definitive pathological outcome confirmed in all cases the FSE outcome. Table 2 underlines surgical and pathological outcomes. Fifty

**Table 1.** Patient's data

| | |
|---|---|
| Age (range) | 67.35 ± 15.45 (51-82) |
| No. clinical T2 (%) | 200 (100) |
| Tumour size (mm) (range) | 31.2 ± 12.11 (12-61) |
| pT2 | 190 (95%) |
| pT3 | 10 (5%) |
| No. glansectomies (%) | 135 (67.5) |
| No. partial penectomies (%) | 65 (32.5) |

**Table 2.** Surgical outcome

| Surgical Procedure | n | MRI Evidence (N Negative; P Positive for Infiltration of CC) | PDU Evidence (N Negative; P Positive for Infiltration of CC) | FSE (N Negative; P Positive for Infiltration of CC) | Definitive Pathological Outcome (n Description) |
|---|---|---|---|---|---|
| Glansectomy | 135 | 133 N<br>2 P | 130 N<br>5 P | 135 N<br>0 P | 135 = pT2 without CC infiltration |
| Partial penectomy | 65 | 17 N<br>48 P | 2 N<br>63 P | 0 N<br>65 P | 55 = pT2 with CC infiltration<br>10 = pT3 |
| Total | 200 | 150 N<br>50 P | 132 N<br>68 P | 135 N<br>65 P | 190 pT2<br>10 pT3 |

CC, corpora cavernosa; FSE, frozen section examination; MRI, magnetic resonance imaging; PDU, penile Doppler ultrasound.

**Table 3.** MRI and PDU related outcomes

| | n | Imaging Outcome | n | Definitive Path. Outcome (n) | Mismatches (n) |
|---|---|---|---|---|---|
| MRI | 200 | Positive for CC infiltration | 50 | 65 | 2 |
| | | Negative for CC infiltration | 150 | 135 | 17 |
| PDU | 200 | Positive for CC infiltration | 68 | 65 | 5 |
| | | Negative for CC infiltration | 132 | 135 | 2 |

Abbreviations as in Table 2.

**Table 4.** MRI and PDU outcomes, accuracy, precision, negative predictive value, sensitivity, and specificity

| | Accuracy (%) | Precision (%) | NPV (%) | Sens. (%) | Spec. (%) |
|---|---|---|---|---|---|
| PDU | 96.5 | 92.6% | 98.4 | 96.9% | 96.2 |
| MRI | 90.5 | 96.0% | 88.6 | 73.8% | 98.5 |
| *P*-value | NS | NS | NS | $P < .05$ | NS |

Abbreviations as in Table 2.

patients were positive for CC infiltration at the MRI, whereas 150 showed no infiltrations. PDU revealed infiltration of the CC in 68 patients with a negative outcome in 132. Table 3 compares infiltrations of the CC revealed by MRI, PDU, and confirmed or not by FSE and definitive pathological outcome. Table 4 underlines MRI and PDU outcomes focused on accuracy, precision, negative predictive value, sensitivity, and specificity.

## DISCUSSION

Penile SCC can be cured in over 80% of all cases but is a life-threatening disease with poor prognosis once metastatic spread has occurred. Furthermore, local treatment, although potentially life-saving, can be mutilating and devastating for the psychological well-being of the patient. Therefore, the treatment of patients with penile cancer requires a careful diagnosis and adequate staging before treatment decisions can be made.[1] The aim of any surgical treatment must be the complete removal of the penile carcinoma and negative surgical margins must be achieved. The width of negative surgical margins should follow a risk-adapted strategy based on tumour grade. Negative surgical margins may be confirmed intraoperatively by FSE.[20] If surgical margins are studied following these criteria (including urethral and periurethral tissue), only 5 mm of tumour-free tissue is sufficient to consider the surgical margins to be negative.[21] Conventional partial penectomy as a treatment for localized SCC is increasingly being replaced by methods that conserve the penis, because of good functional and cosmetic results.[14,15] However, the accurate selection of patients amenable for organ sparing therapy is needed to avoid high recurrence rates. Therefore, the extension of the primary carcinoma must be assessed with great care. In all cases where the diagnosis is clinically uncertain or when nonsurgical treatment is planned, histological verification must be obtained before treatment.[1] For all surgical treatment options, the intraoperative assessment of surgical margins by FSE is recommended as tumour-positive margins lead to local recurrence.[17] Glansectomy does have the lowest recurrence rate among the treatment modalities for small penile lesions[17,18,22] which do not infiltrate CC. If a CC infiltration (with or without urethral involvement) is present, partial penectomy is a feasible option.[1] Several studies reported this technique as safe in T2 and T3 patients.[23-25] If organ sparing approach is planned and preoperative decisions are needed to set up a proper patient counselling on the surgical strategy to be adopted, MRI in combination with an artificial erection with prostaglandin E 1 is used to exclude tumour invasion of the CC.[9,10] Despite the cost of MRI (that is certainly higher than PDU), this test cannot be used in all

patients because of relative or absolute contraindications to this test. Any of the following situations could be a potential contraindication for an MRI: the presence of artery stents, vascular clips, foreign bodies, vena cava filters, prosthetic heart valves, aortic stent grafts, temporary pacing devices, implantable cardioverter defibrillator, tattoo or permanent makeup, known claustrophobia, any type of prosthesis, ear implants, renal impairment.[26] The main part of these conditions grows up in incidence during the sixth decade in which penile SCC raises its peak.[3] A cheaper test that could reveal a CC infiltration is PDU and it has been already tested in previous studies.[11,12] In the present study, PDU was similar for assessing tumour infiltration compared with MRI (Table 4). Furthermore, a PDU predicted CC infiltration with the highest sensitivity (96.9%) ($P$ <.05) and was accurate (96.5%) for determining the presence of deep infiltration, missing substantial infiltration in only 2 of 200 patients (Table 3). There were 5 false-positive findings of infiltration. The possible reason for this relatively higher rate compared with MRI could be explained with the thinness of the CC margin that in the ultrasound field needs a certain expertise to be detected. Cavernosal infiltration was identified accurately by ultrasonography in previous reports,[11,12] and this study confirms that outcomes. A previous study by Lont et al[27] underlined how PDU seemed to be a less reliable method for determining such infiltration. This was a result of the relatively many extensive infiltrating tumours with poor delineation of the CC in that cohort of 33 patients. When less extensive tumours were considered, PDU could detect infiltration depth and CC infiltration more accurately. MRI is the current method for determining CC infiltration[1] but at the cost of some false-negative results mainly in T2-weighted images. As stated before, on the other hand, MRI can reveal a much more higher false-negative rate of infiltration in T2-weighted images because the CC border is here better evidenced and its appearance can hide a millimeter infiltration. As it is known, sensitivity and specificity are peculiar features of the test employed, whereas positive predictive value (precision) and negative predictive value are thus affected by disease incidence. In this study, PDU revealed an evident statistical better sensitivity compared with the one of MRI. The reason of this statistical evidence is clearly driven by the 17 MRI false negative compared with the only 2 for PDU in detecting CC infiltration. On the other hand, to reach this results, PDU needs a senior PDU skilled urologist to perform the test on the selected patients, and this can be regarded as a limitation. Another limitation that needs to be underlined is the use of a 1.5 T MRI machine. It is possible to say that MRI outcomes have been improved if a 3 T MRI machine could have been used, thus enhancing spatial and contrast resolution. Despite the fact that one nomogram by Solsona[28] was used to estimate patients' prognosis, it will be necessary to analyse the evidence about the cancer-related follow up of this cohort of patient in the next years. So is there a role for imaging in determining which patients can undergo organ sparing treatment? SCC can be accurately staged by a PDU, whereas its outcome should be definitively confirmed by FSE. In our experience, the high sensitivity of PDU can be of help in patients in whom the extent of infiltration into the CC cannot be determined properly by 1.5 T MRI. Because of the high sensitivity for cavernosal infiltration and its precision in determining infiltration depth, PDU could become the imaging method of choice. Images in the sagittal plane are particularly useful for detecting the proximal extent of the tumour; knowing the proximal extent enables the surgeon to determine an optimal level of penis amputation with adequate tumour-free margins.

## CONCLUSION

PDU is reliable for estimating SCC infiltration of CC and has a better sensitivity compared with 1.5 T MRI. It is a less expensive examination and can be used to counsel patient and drive surgical strategy. Its role is surely operator dependent. Further studies are needed to compare PDU with 3 T MRI.

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