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Review Article

Evaluation of the Oncological Outcomes According to Different Organ-Sparing Techniques in Penile Cancer

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Introduction

Penile cancer represents 1% of malignant neoplasms in men [1]. A large epidemiological study revealed that 65.4% of penile cancer are localized, 26.5% are locoregional and 3.5% are metastatic at the time of diagnosis [2]. Surgical amputation is considered the standard treatment but results in physical and psychological deterioration with a negative impact on quality of life [1]. Organ-Sparing Surgery (OSS) such as wide local excision, circumcision, glans resurfacing, partial or total glansectomy and partial penectomy, preserving penile appearance, sexual and voiding function, in addition to resulting in excellent local control with low recurrence rates [1,3]. There is no clear evidence about the ideal surgical margin, however in lower-risk tumors minimal section margins > 1 mm and in higher-grade lesions wider margin around 3-5 mm can be considered safe according to the literature [4,5]. Furthermore, Local Recurrence (LR) has little influence on long-term survival, although there may be challenges in optimal patient selection and counseling for this approach [6]. Historically a 3-4 cm penile stump length after OSS appears to be suitable for maintenance of voiding function [7]. We aimed to analyze the local recurrence according to different OSS techiniques in the treatment of Penile Squamous Cell Carcinoma (pSCC) and evaluate the impact in oncological outcomes.

Materials and Methods

We retrospectively queried institutional databases for OSS (wide local excision, circumcision, glansectomy and partial penectomy) and baseline patient characteristics (age, tumor location, tumor size, tumor grade, T stage, nodal status, vascular invasion, lymphatic invasion and perineural invasion) between January 2016 and August 2023. Subsequently, the LR rate was determined according to OSS techniques and evaluated the impact of local recurrence on survival outcomes (PFS local disease, PFS regional lymph nodes disease, PFS distant disease and overall survival) using Kaplan-Meier survival. Surgical techniques and lymph node staging in cN0 disease and management in cases of nodal disease were performed according to established guidelines at the time of treatment. Although the role of frozen section and its value in the interpretation of excision margins remains uncertain, all patients underwent intra-operative frozen section. According to the number of risk factors present in each patient, we stratified patients into three risk categories: low-risk (no risk factors), intermediate (one risk factor) and high risk (two or more risk factors) . From 71 cases

of histologically confirmed pSCC, 7 were submitted to radical penectomy and were excluded from this study, being a cohort of 64 cases submitted to OSS. This project was formally approved by the local research ethics committee (Cassiano Antônio Moraes University Hospital of the Federal University of Espirito Santo; Number: 5.445.012).

Results

A total of 64 patients fulfilled the study's inclusion criteria. The mean (SD) age at presentation to our center was 57.8 (25 - 86) years. Of the 64 patients who underwent OSS, 3 patients underwent circumcision, 6 underwent wide lesion excision, 18 underwent glansectomy and 37 patients underwent partial penectomy. All patients underwent intra-operative frozen section. The baseline characteristics of the cohort are shown in (Table 1) In this cohort of patients treated with OSS we showed good local oncological control, with local recurrence rates of 12.5%. LR were reported in 1 case (33%) in the circumcision group, 3 patients (17%) of the glansectomy group and 4 patients (11%) in the partial penectomy group. None of patients submitted to wide lesion excision presented local recurrence. (Table 2). The different OSS techniques were not associated with a negative impact on the LR rate (p = 0.4).

Characteristic	**Overall**, N = 64	**WIDE LOCAL EXCISION** N = 6	**GLANSECTOMY** N = 18	**PARTIAL PENECTOMY N = 37**	**CIRCUNCISION** N = 3	**p-value** [1]
Age, Median (IQR)	57 (50 – 69)	70 (59 – 73)	56 (42 – 69)	56 (51 – 63)	72 (66 – 74)	0.14
Ethnicity, n (%)						0.82
White	18 (28)	2 (33)	7 (39)	8 (22)	1 (33)	
Brown	33 (52)	3 (50)	7 (39)	21 (57)	2 (67)	
Black	13 (20)	1 (17)	4 (22)	8 (22)	0 (0)	
Size (cm), n (%)						<0.001
<1	3 (4.7)	0 (0)	3 (17)	0 (0)	0 (0)	
01-Feb	23 (36)	4 (67)	10 (56)	7 (19)	2 (67)	
03-Apr	23 (36)	1 (17)	5 (28)	16 (43)	1 (33)	
>4	15 (23)	1 (17)	0 (0)	14 (38)	0 (0)	
Tumor grade, n (%)						0.74
G1	38 (59)	4 (67)	11 (61)	21 (57)	2 (67)	
G2	21 (33)	2 (33)	6 (33)	13 (35)	0 (0)	
G3	5 (7.8)	0 (0)	1 (5.6)	3 (8.1)	1 (33)	
T stage, n (%)						0.88
Tis	3 (4.7)	0 (0)	1 (5.6)	2 (5.4)	0 (0)	
T1	20 (31)	1 (17)	6 (33)	13 (35)	0 (0)	
T2	28 (44)	3 (50)	7 (39)	15 (41)	3 (100)	
T3	13 (20)	2 (33)	4 (22)	7 (19)	0 (0)	
N stage, n (%)						0.079
NA	59 (92)	5 (83)	17 (94)	35 (95)	2 (67)	
N0	2 (3.1)	0 (0)	0 (0)	2 (5.4)	0 (0)	
N2	3 (4.7)	1 (17)	1 (5.6)	0 (0)	1 (33)	
Vascular invasion, n (%)						0.9
No	51 (80)	5 (83)	14 (78)	30 (81)	2 (67)	
Yes	13 (20)	1 (17)	4 (22)	7 (19)	1 (33)	

Lymphatic invasion, n (%)						0.14
No	63 (98)	5 (83)	18 (100)	37 (100)	3 (100)	
Yes	1 (1.6)	1 (17)	0 (0)	0 (0)	0 (0)	
Perineural invasion, n (%)						0.21
No	50 (78)	4 (67)	15 (83)	30 (81)	1 (33)	
Yes	14 (22)	2 (33)	3 (17)	7 (19)	2 (67)	
Tumor location, n (%)						0.64
Foreskin	7 (11)	0 (0)	4 (22)	3 (8.1)	0 (0)	
Gland	46 (72)	5 (83)	12 (67)	27 (73)	2 (67)	
Shaft	11 (17)	1 (17)	2 (11)	7 (19)	1 (33)	
[1] Kruskal-Wallis rank sum test; Fisher's exact test						

Table 1: Baseline patient characteristics.

Characteristic	**Wide lesion excision**	**Circumcision**	**Glansectomy**	**Partial penectomy**	**p-value**
	N=6	**N=3**	**N=18**	**N=37**	
Local Recurrence					0.4
No	6 (100%)	2 (67%)	15 (83%)	33 (89%)	
Yes	0 (0%)	1 (33%)	3 (17%)	4 (11%)	
n (%)					
Fisher´s test					

Table 2: Local recurrence rate according to the different surgical techniques for penile preservation.

The different OSS techniques were not associated with a negative impact on PFS local disease (p=0.69), PFS regional lymph nodes disease (p=0.28), PFS distant disease (p=0.82) and overall survival (p=0.14) (Figure 1).

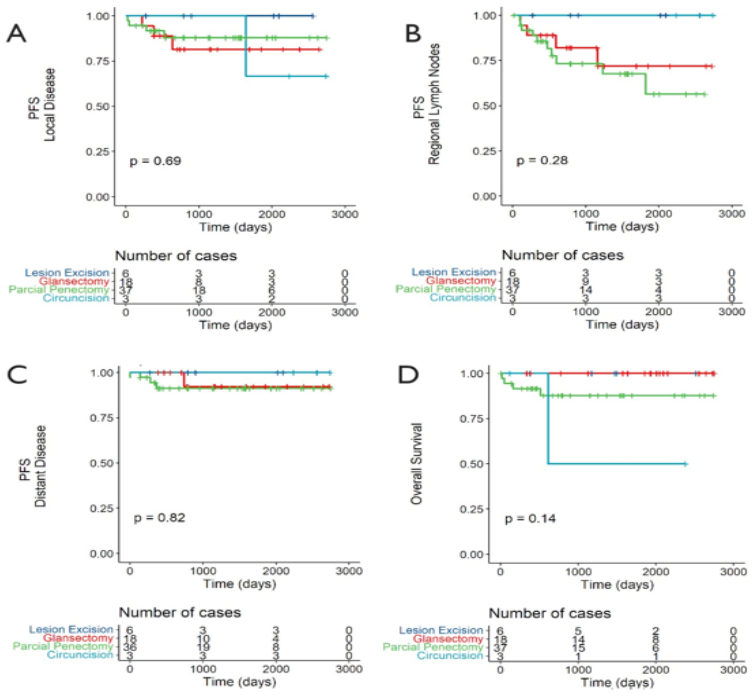

Figure 1: Kaplan–Meier curves showing the effect of Local Recurrence (LR) on (A) PFS local disease, (B) PFS regional lymph nodes disease, (C) PFS distant disease and (D) overall survival, stratified into four groups according to the different surgical techniques for penile preservation.

After stratification according to the number of risk factors, 38 (59.3%) patients were classified as low risk, 21 (32.8%) intermediate risk and 5 (7.9%) high risk. All patients who had local recurrence during follow-up had at least one poor prognostic factor. The 8 patients belonged to the intermediate risk group, and the most prevalent factor was lymph vascular invasion, present in 75% of the cases that evolved with local recurrence (Table 3).

	Low risk	Intermediate risk	High risk
Risk stratification	38 (59.3%)	21 (32.8%)	5 (7.9%)

Table 3: Stratification according the number of risk factors: low-risk (no risk factors), intermediate (one risk factor) and high risk (two or more risk factors).

Discussion

Penile cancer is a rare disease in most developed countries, but has one of the highest prevalence in Brazil [8]. The concept of OSS is based on how the distance from the tumor to the margin affects LR. The aim of primary tumor treatment is complete removal, while ensuring organ and functional preservation without compromising the oncologic outcome. Agrawal A et al. demonstreted that most lesions do not spread > 5 mm beyond the macroscopic margin. In addition, subsequent reports showed that an excision margin of between 5 and 10 mm results in acceptably low recurrence rate [9]. More recently, a study by Sri D et al. found that local recurrence rates increased considerably only when the distance from the tumor to the margin was < 1mm [10]. High-grade disease, Lymphovascular Invasion (LVI), and pT3 stage have been proposed as independent predictors of local recurrence and this may potentially have led to adoption if a risk or grade based approach to resection margins [6]. OSS is the standard treatment for distal penile cancer. It offers excellent local control with low recurrence rates and, in most cases, sexual and voiding function are possible goals to be achieved [11]. Over 80% of tumours are amenable to OSS techniques [7]. OSS should be considered in patients with stages Tis/Ta/T1 (Carcinoma in situ/ Non-invasive verrucous carcinoma/tumor invades sub epithelial connective tissue with lymph vascular invasion or perineural invasion)

and some T2 (tumor invades corpus spongiosum with or without invasion of the urethra) mainly when there is no invasion of the urethra and a well or moderately differentiated PC. A few with Stage T3 (tumor invades the corpora cavernosa with or without invasion of the urethra) may be considered for OSS when urethral involvement is confined to the glans and full excision of the glans is performed. The patient should have a penile stump that is sufficient for forward directed urine flow in an erect position and the suggested penile length to maintain urinary function is 3-4 cm [11]. The management of regional LNs is decisive for patient survival. Patients without palpable inguinal nodal disease on physical examination may undergo active surveillance, as long as Tis, Ta G1, T1G1, whereas tumors > T1G2 should undergo bilateral inguinal Lymphadenectomy (ILNF).

ILND remains the standard of care for patients with cN1–2 and in pN1disease ILND is curative with equivalent outcomes in those patients without nodal disease. Given the very high chance of recurrence, enlarged fixed inguinal LNs (cN3) or clinically evident pelvic metastases require multimodal treatment by induction chemotherapy and consolidative surgery in responding patients. Pelvic nodal disease does not occur without ipsilateral inguinal LN metastasis [12,13]. Importantly, several series have shown the lack of negative impact on survival of local recurrence after OSS, which has been the main driver of guideline recommendations for this approach [7,10]. Djajadiningrat et al. studied a large cohort comparing OSS (including laser photocoagulation, circumcision, wide local excision, glans resurfacing and glansectomy) vs partial and total penectomy, and found no difference in Cancer Specific Survival (CSS) between the two groups, concluding that the use of OSS does not affect oncological outcomes [14].A large European two-centre study of 415 patients, spanning 50 years from 1956, showed LR rates of 27.7%. However, they did find that LR did not significantly impair survival with a 92% 5-year cancer-specific survival rate in their cohort [10]. Smith et al. report a 4% LR rate in 72 patients treated with glansectomy for pT1 and pT2 pSCC, which is quite low [15].Conversely, more recent studies incline towards higher-risk tumours and show higher rates of LR [16]. In this cohort of patients treated with OSS we showed good local oncological control, with local recurrence rates of 12,5% which is consistent with the LR rate in the present multicentre cohort (10.5%) [16]. Similar to reported by Tang et al. and Danakas AM et al., the present cohort was enriched for pT2 or higher disease (> 65% of patients) [15,16] . Most LR occurred in the first 2 years after surgery in the present study, which is according to previous reported studies, marking the importance of stringent follow-up after OSS to ensure early detection of LR. In contrast to those findings, a large retrospective study by Roussel E et al. of a multicenter cohort including 230 pT1, 534 pT2, and 108 pT3 cases treated in high-volume centers with glansectomy with or without distal corporal tip resection revealed that the 5-yr CSS rate was only 68.0% for patients who experiencedlocal recurrence, compared to 93.1% for those who did not [6]. In this cohrt OSS is not associated with a negative impact on PFS local disease, PFS regional lymph nodes disease, PFS distant disease and overall survival. Performing intra-operative frozen section during penectomy does not appear to have any significant impact on final surgical margins status and long-term oncologic outcomes. However, in select patients may benefit from the routine frozen section [17]. In this cohort, all patients underwent intra-operative frozen section witch resulted in a 100% surgical margin.There is a lack of good-quality studies concerning sexual, functional, and psychological patient outcomes after OSS. A recent retrospective analysis of 34 patients who underwent glansectomy examined urinary and sexual outcomes using validated questionnaires such as the IIEF and International Prostate Symptom Score (IPSS Score) showed that sexual and urinary functions were not affected by glansectomy and advocated for the use of this technique [18].

Limitations

The main limitation of our study is the small number of cases and a retrospective database analysis.

Conclusion

OSS remain a safe and viable option for the treatment of localized pSCC. Although associated with a higher risk of local recurrence, there is controversy over the impact of local recurrences on outcomes. In this cohort of patients treated with OSS, the different surgical techniques for penile preservation were not associated with a negative impact on the local recurrence rate ($p = 0.4$) and on local recurrence-free survival ($p = 0.7$). All patients who had local recurrence during follow-up had at least one poor prognostic factor and the most prevalent factor was lymph vascular invasion. Strict postoperative clinical surveillance is essential for early detection of possible recurrence.

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