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Oncologic outcomes and subsequent treatment following organ sparing surgery for penile carcinoma: The University of Texas M.D. Anderson Cancer Center Experience

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Abstract

Objectives: To determine the oncologic outcomes of organ sparing surgery (OSS) for penile cancer and to determine the management of and risk factors for local recurrence at a tertiary referral center in the United States.

Methods and Materials: Patients undergoing OSS from 1996 to 2018 at The University of Texas, MD Anderson Cancer Center were identified using a prospective database. Organ sparing procedures included: wide local excision (WLE; including circumcision and glans resurfacing), partial or total glansectomy, laser therapy, or OSS combined with laser ablation (i.e., laser combination). Clinical and pathologic data were collected for descriptive analysis. Recurrences (local and regional) were identified, and the association between overall and local recurrences was determined using Cox proportional hazards regression. Overall and recurrence free survival analyses were performed using Kaplan-Meier estimates.

Results: A total of 129 patients undergoing OSS were identified with a median follow up interval of 28.0 months. The most common OSS was laser combination (38.8%), and 65.1% of patients presented with pTis or ≤pT1a disease. Twenty (15.5%) recurrences were identified, of which 17 (13.2%) were local and 3 (2.3%) were regional. There were no distant recurrences as the initial site of recurrence. The median time to local recurrence was 20.9 months, and 88.2% were identified within 5 years of surgery. Most (76.5%) local recurrences were successfully treated with further penile preservation without a detrimental impact on overall survival. Patients with pathologic Ta or T1a disease treated with laser or laser combination surgery were more likely to present with local recurrence.

Conclusion: OSS using a variety of techniques to achieve negative surgical margins provides long-term effective local control for localized penile cancer. Most local recurrences can be successfully treated with further penile preserving strategies and long follow-up is essential. Laser therapy or laser combination with OSS should be used with caution in patients with invasive penile cancer.

1. Introduction

The American Cancer Society estimates that 2200 new cases of penile cancer will be diagnosed in the United States in 2020 [1].Traditionally performed partial or total penectomy have been associated with significant comorbidity with respect to altered voiding, sexual function, appearance, and psychological well-being [2-3] and radiotherapy has been associated with significant adverse events and higher rates of recurrence [4]. Organ sparing surgery (OSS) is increasingly utilized in patients with low grade, lower stage, distal tumors, and may also be an option for select patients with higher grade/stage tumors that are limited to the glans or foreskin [5-12]. OSS describes a variety of surgical techniques that include glans resurfacing, Moh's microsurgery, wide local excision (usually referring to skin lesions), laser ablation, and partial or total glansectomy. The feasibility of

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OSS has become manifest since the traditional "2 cm margin" has been challenged by recent reports, which now suggest that even a 1 mm tumor free surgical margin may achieve effective cancer control [13-15].

Single center series describing OSS approaches where margin distances of less than 2 cm were routinely obtained suggest acceptable overall and cancer specific survival for appropriately selected patients. However, there are few prospective larger patient series in the literature in this rare cancer site. Herein, we describe our experience and outcomes in performing OSS for penile carcinoma at our tertiary referral center over a 22-year period utilizing our prospectively maintained database. Further in virtually every case our surgical protocol mandated achieving negative surgical margins prior to the case being concluded. The primary endpoints were to determine the incidence, management of, and risk factors for local recurrence (LR) following OSS. We also performed survival analyses as well as described regional and distant recurrences.

2. Methods

Institutional review board approval was obtained. 129 patients with biopsy proven penile carcinoma undergoing OSS at The University of Texas, MD Anderson Cancer Center (MDACC) between January 1996 and 2018 were identified in our department penile cancer database. During the same time period at our center, we performed 166 partial penectomies and 46 radical/total penectomies. Thus the 129 organ sparing procedures that were performed represented 37.8% of the total ($n = 341$). The data for 16 patients was retrospectively collected from 1996 to 2004. Beginning in 2004, 113 patients were prospectively entered. Variables collected in the database are listed in Suppl. Table 1. Patients with primary carcinoma of the urethra, nonsquamous histology and those treated with partial or radical penectomy were excluded from analysis. LR was defined as disease relapse on the penis following OSS at The University of Texas, MD Anderson Cancer Center after the primary procedure. Regional recurrence was defined as newly diagnosed nodal metastases not present at time of OSS.

OSS was chosen as primary treatment for patients with lesions in a favorable location including the glans penis, foreskin or shaft skin. Patient preference was also a consideration, and in our experience the vast majority of patients choose OSS when feasible. Case selection was limited to patients where complete excision of the lesion where negative margins would be possible while maintaining the length of the penile corpora. Patients with gross involvement of the corpora cavernosum were excluded. Since 2011 we have routinely performed magnetic resonance imaging (MRI) with a dedicated penis protocol to aid in determining the extent of invasion. Inguinal lymphadenectomy was performed in patients deemed to be at high risk for nodal metastasis, based on pathological staging, clinical examination, or imaging findings. The goal of treatment was to obtain local tumor control while maintaining penile length and function to the extent dictated by negative surgical margins.

Patient selection and choice of OSS type were at the discretion of the treating surgeon (CAP, MA, and JP). OSS procedures included: wide local excision (WLE, including circumcision or glans resurfacing), partial or total glansectomy, Potassium titanyl phosphate (KTP) or Carbon Dioxide (CO2) laser ablation alone, and KTP or CO2 laser combination with secondary OSS procedure (laser combination).

Table 1
Patient Clinical and Pathologic Baseline Characteristics

Characteristic	*n* (Total *n* = 129)	%
Median age (IQR)	61.5 (53.1-70.2)	100
Median tumor size (mm; IQR)	20 (1.5-80)	100
Lesion location		
Glans	55	42.6
Shaft	37	28.7
Glans+foreskin	19	14.7
Foreskin	12	9.3
Glans+shaft	6	4.7
Pathologic T stage		
pTis	43	33.3
pTa	2	1.6
pT1a	39	30.2
pT1b	27	20.9
pT2	18	14.0
pT3 or 4	0	0
Pathologic grade		
Not reported	13	10.1
Not applicable (CIS)	43	33.3
Well or moderately differentiated	38	29.5
Poorly differentiated	35	27.1
Lymphovascular invasion		
Yes	10	7.8
No	119	92.2
Clinical N stage		
cN0	112	86.8
cN1	10	7.8
cN2	5	3.9
cNx	2	1.6
Lymph node dissection		
Yes	33	25.6
No	96	74.4
Pathologic N stage		
pN0	25	19.4
pN1	2	1.6
pN2	1	0.8
pN3	5	3.9
pNx	96	74.4
Margin status		
Negative	128	99.2
Positive	1	0.8
Recurrence		
Yes	20	15.5
No	109	84.5
Recurrence site (initial)		
Local	17	85
Regional	3	15
Distant	0	0

IQR=interquartile range; OSS=organ sparing surgery

When using either laser 5% acetic acid was routinely utilized to treat the index lesion and adjacent areas that stained "white." The KTP laser was preferentially utilized with the CO2 laser infrequently employed and only in cases of pTis given its lower depth of penetration. WLE was utilized in the case of penile shaft skin lesions to completely excise areas of invasive or in situ carcinoma. Glans resurfacing was used as previously described [9]. Partial glansectomy was utilized when the excised area would result in at least 60% of residual glans penis with the goal of maintaining sensation (see photo). When partial resection could not be achieved to remove all invasive disease with an adequate amount of residual glans remaining a total glansectomy was performed. Intraoperative frozen sections were obtained for virtually all OSS cases. For cases where residual invasive disease was identified further resection was undertaken until a negative frozen section was achieved. For cases where frozen section analysis revealed residual carcinoma in situ (CIS; penile intraepithelial neoplasia PeIN, especially on the glans margin of resection), the patient was treated with intraoperative KTP laser therapy (with biopsy of the underlying dermis) to achieve a negative margin. Primary tumor pathology was reviewed by dedicated genitourinary pathologists (PT, PR), and all tumors were reclassified according to the American Joint Cancer Commission (AJCC) 8th edition staging [16].

2.1. Statistical analysis

Patient characteristics were summarized using descriptive statistics, summarized in Table 1. Pathologic stage of primary tumor was stratified according to low risk disease (pTis, pTa or pT1a) and high risk disease (≥ pT1b) related to potential to metastasize to the inguinal lymph nodes [17]. Recurrence location was stratified according to location (local vs. regional vs. distant). The distribution of each continuous variable was summarized by its median and interquartile. The distribution of each categorical variable was summarized in terms of its frequencies and percentages. Kaplan-Meier curves were used to estimate time-to-event variables. The overall survival (OS) was defined as the time from procedure until death or last follow-up. The recurrence free survival (RFS) was defined as the time from procedure until any recurrence or last follow-up/death (death was not considered as recurrence event). The local RFS is defined as the time from procedure until LR or last follow-up/death (death was not considered as a recurrence event). Log rank tests were used to compare each time-to-event variable between groups. The Cox proportional hazards regression model was used to evaluate the ability of patient prognostic variables to predict each of OS and RFS. Clinical factors examined to predict risk for recurrence included: lesion location (glans, shaft, glans+foreskin, foreskin, glans +shaft), cN stage, procedure type (WLE, partial or total glansectomy, laser, laser combination), grade, pT stage and pN stage. p values < 0.05 was considered statistically significant. Splus software (TIBCO software Inc, Pale Alto, CA) and SAS software 9.2 (SAS Institute, Cary, NC) were used for statistical analysis.

3. Results

3.1. Patients and organ sparing procedures

Baseline patient characteristics are summarized in Table 1. Most patients had low risk disease on pathology (65.1%) and presented with clinically negative inguinal nodes (86.8%). Table 2 lists the procedures performed and the associated recurrences. The most commonly performed procedure was OSS combined with a laser procedure (38.8%). Only one patient had a positive surgical margin noted on final pathology.

3.2. Recurrences

Twenty patients (15.5%) were identified with recurrence at the time of data censoring at a median time to recurrence of 18.9 mos. (range 2.2-136.7). Of these, 17 (13.2%) presented with a LR at a median recurrence free interval of 20.9 mos. (range 2.2-136.7). Treatment and outcomes of LRs are listed in Table 3. Ten patients (58.8%) with LR were successfully treated with OSS and are without evidence of disease (NED). Three patients were treated with partial penectomy and are NED. The remaining four patients underwent radical penectomy, one of which developed distant metastases and died of disease. Overall, 76.5% of patients with LR were successfully treated with further penile preservation (OSS and partial penectomy). Among this cohort the median follow-up from time of recurrence diagnosis to last known follow up was 32.5 months (range 0-153.1).

Three patients presented with a regional recurrence at a median time of 3.0 mos (range 2.4-17.0). Two were treated with a complete LND and are NED. One patient developed distant metastases following complete LND and was treated with palliation. There were no patients that had a distant recurrence as the initial site of recurrence in this series. In this series 3% of patients exhibited a distant failure at a subsequent site of disease but only after a prior local or regional failure (Suppl Table 2).

Table. 2
Organ Sparing Surgery Techniques and Outcomes

Procedure type	No. Procedures	No. Recurrences (% procedure type)	
	(% total)	Local ($n = 17$)	Regional ($n = 3$)
Wide local excision[a]	36 (27.9)	2 (5.6)	0
Partial or total glansectomy	35 (27.1)	3 (8.6)	1 (2.9)
KTP or C02 laser alone	8 (6.2)	2 (25.0)	0
OSS combined with KTP laser	50 (38.8)	10 (20.0)	2 (4.0)
Total	129	17	3

[a] One patient in this group had glans resurfacing

Table 3
Treatment of Local Recurrences and Outcomes

Patient no.	Treatment	Outcome
1	Partial penectomy/urethrectomy	Second recurrence on penile shaft treated with radical penectomy; pulmonary metastases; patient dead of disease
2	Partial penectomy/glansectomy	NED
3	KTP laser	NED
4	Punch biopsy/KTP laser	Second recurrence distal urethra/skin treated with partial penectomy; third recurrence on distal penile stump treated with radical penectomy/chemotherapy; NED
5	Glansectomy	NED
6	Radical penectomy	NED
7	Partial glansectomy	NED
8	Wide local excision	NED
9	Glans resurfacing	NED
10	Partial glansectomy	Second recurrence on shaft treated with KTP laser/WLE; NED
11	Glansectomy	NED
12	Partial glansectomy	NED
13	Partial penectomy	NED
14	Partial glansectomy	NED
15	Partial penectomy/complete LND	NED
16	Topical therapy	NED
17[a]	Radical penectomy/complete LND	NED

NED: no evidence of disease; ILND: inguinal lymph node disease
[a] Patient presented with local recurrence and a palpable inguinal node

3.3. Follow-up and survival

Median follow up for the entire cohort was 28.0 mos. (range 0.17-188.2). 66 patients (51.2%) had a median follow-up greater than 24 mos. Among these latter patients 15 (22.7%) presented with a LR (compared to 13.2% in the overall cohort). This group had a median follow-up of 72.9 mos. (range 25.1-188.2) and a median recurrence free interval of 21.1 mos. (range 7.5-136.7). LR was diagnosed within 5 years of initial OSS in 15 of 17 patients (88.2%), and within 2 years in 10 of 17 patients (58.8%). Median OS and RFS were 136.7 and 137.5 mos., respectively. The 5

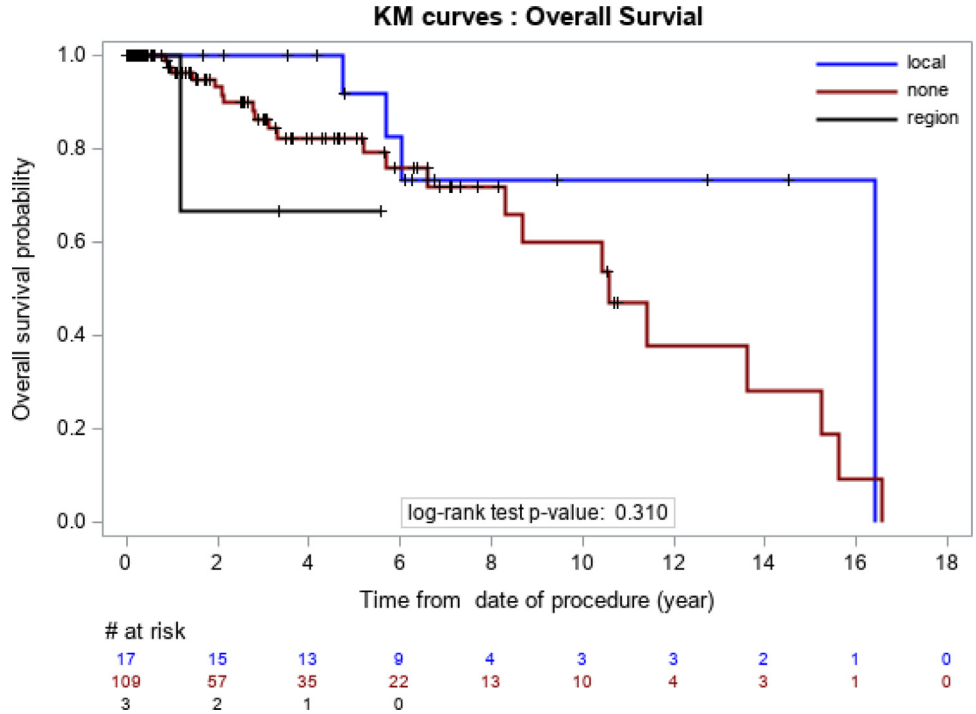

Fig. 1. Kaplan-Meier estimates of overall survival stratified by recurrence status.

and 10-year LR free survival rates were 76% (95% confidence interval [CI]: 0.66, 0.89) and 73% (95% CI: 0.61, 0.87), respectively. The 5 and 10-year OS rates were 83% (95% CI: 0.75, 0.92) and 62% (95% CI: 0.48, 0.8). There was no difference in OS between patients presenting with local or regional recurrence vs. no recurrence (Fig 1).

3.4. Predictors of recurrence

Results of univariate analyses are reported in Suppl. Tables 3 and 4. On univariate analysis, pathologic T stage was the only predictor of local and overall RFS (P= 0.008 and $P = 0.01$, respectively). The K-M plot demonstrating differences in local RFS between the pathologic stages is depicted in Fig. 2 (log-rank $P = 0.008$). Patients with pTa/pT1a disease had worse local RFS compared to those with pTis (Suppl. Fig. 1A, $P = 0.005$), and trended toward worse (but not significantly greater) when compared with those with ≥pT1b disease (Suppl. Fig. 1B $P = 0.065$). There were no differences in local RFS between patients with pTis and ≥pT1b disease (Suppl. Fig. 1C, $P = 0.31$). When OSS procedures were grouped according to excisional (WLE, partial/total glansectomy) or laser/laser and other OSS combination, use of laser treatment was associated with increased risk of LR ($P = 0.0346$).

We performed further analysis to explore possible reasons for the increased risk of LR in patients with pTa/pT1a disease. First, we determined that patients in the pTa/pT1a group were more likely to undergo laser or laser combination therapy than an excisional procedure alone compared to patients in the ≥pT1b group (53.7% vs. 26.7%), and similar to those in the pTis group (53.6% vs. 55.8%, log-rank $P = 0.0087$, Suppl. Table 5). Of patients undergoing laser or laser combination therapy, those in the pTa/T1a group had worse local RFS than those with pTis (Supplementary Figure 2A, $P = 0.003$). However, there was no difference in local RFS between pTa/pT1a disease and pTis in patients undergoing an excisional procedure (Supplementary Figure 2B, $P = 0.768$). Likewise, patients with pTa/T1a disease treated with laser or laser combination had worse local RFS than those treated with excisional surgery (Fig. 3A, $P = 0.03$). This trend was not observed in the pT1b or pTis group (Fig. 3B and C). Together, these results suggest that the association between increased risk of LR and pTa/pT1a disease may be attributable to the use of a laser in this group.

4. Discussion

Among sexually active men and those desiring to maintain penile form and function the use of organ sparing techniques in the treatment of penile cancer is desirable, as radical and partial penectomy are associated with significant quality of life related comorbidity [3,18]. OSS has become more feasible since the traditional “2cm margin approach” has been challenged by multiple reports [13-15]. As a result, outcomes of OSS are appearing in the literature,

Table. 4
Summary of OSS Series

Series	No. pts	Procedures	Pathology (%)	No. involved margins (%)	Incidence of local recurrence	Time to local recurrence (months)	Follow-up (months)
Minhas et al [14]	51	WLE, glans excision (partial or total), partial penectomy	Tis (5.9), T1 (39.2), T2 (51.0), T3 (3.9)	3 (5.9)	2 (4%)	NR	26 (2-55) median
Smith et al [12]	72	Glansectomy + STSG	T1 or T2 limited to glans	6 (8.3)	3 (4%)	NR	27 (4-68) mean
Feldman et al [5]	56	WLE, partial glansectomy, circumcision, topical therapy, Moh’s microsurgery	CIS (50), T1 (50)	12 (21.4)	12 (21.4)	51.4	51.36 (6-132)[a] mean
Philippou et al [8]	179	Circumcision, WLE, glansectomy, partial penectomy	T1 (49.0), T2 (38.0), T3 (12.8)	12 (6.7)	16 (8.9)	26.1	39 (4-107) median
Veeratterapillay et al [6]	65	Total and partial glansectomy, glans relining and distal penectomy	Tis (20.0), T1 (47.7), T2 (29.2)	10 (15.4)	4 (6.0)	15.0	40 (12-72) mean
Djajadinangrat et al [7]	451	Laser, local excision, glans resurfacing	T1 (56.0), T2 (42), T3 (2)	97 (22)	122 (27.0)	10.0	65.0 (41-101) median
Baumgarten et al [20]	1188	Circumcision, glansectomy, WLE, laser with local excision, laser alone, glans resurfacing	Tis (17.0), Ta (1.3), T1 (48.5), T2 (33.2)	190 (16)	234 (19.7)	16.3	43.0 (27.9-60.4) median
Present series	129	WLE, partial or total glansectomy, laser alone, combination OSS + laser	Tis (33.3), Ta (1.7), T1 (51.1), T2 (14)	1 (0.78)	17 (13.2)	20.9	28.0 (0.17-188.2) median

OSS: organ sparing surgery; STGS: split thickness skin graft; WLE: wide local excision.
[a] patients with less than 6 months of follow-up excluded from analysis

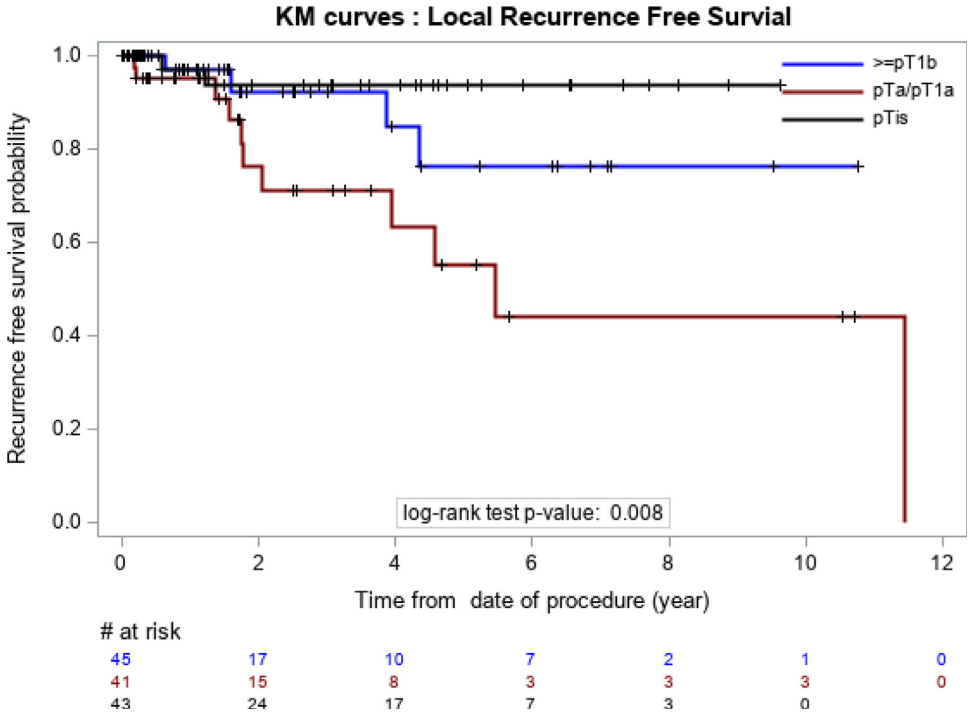

Fig. 2. Local recurrence free survival stratified by pathologic stage

with most series reporting less than 100 patients (Table 4). The 2 largest series include 451 and 1,188 patients, respectively [7,20]. These studies are limited by their historical perspective (cases dating back to the 1950s) and variability of treatment, expertise, and documentation that exists with large multi-center cohorts. Furthermore, frozen section margins were not routinely obtained. A large single center series including 179 patients treated with a variety of organ sparing techniques reported an overall recurrence rate of 24.6% with a LR rate of 8.9% at a mean follow-up of 42.8 months [8]. Overall, the literature suggests a higher rate of recurrence for OSS compared to traditional amputations, which is reported to be approximately 4% [4,7]. The LR rate for more aggressive OSS excisional strategies ranges from 4-8.9% [4, 6, 10,12], while for less invasive OSS strategies (i.e., laser, Moh's, local excision etc.) it ranges from 13.2 to 27% [3,5,19, present series]. Despite the increased recurrence with OSS when compared with traditional amputation, there does not appear to be a detrimental impact on OS, as there was no difference in OS between patients presenting with or without LR in this series or others [21].

Recurrence location is the most important predictor of survival following treatment of the primary tumor in penile carcinoma. In a large series of 700 patients treated with a combination of OSS and radical surgery, 205 patients presented with a recurrence, of which 18.6% were local [22]. The 5-year disease specific survival for local, regional, and distant metastases was 92%, 33% and 0%, respectively [22]. In our series, 94% of patients presenting with LR had no evidence of disease at a median follow-up of 35.33 mos. (range: 0-153.1) following detection and management of the recurrence. Furthermore, the majority (76%) were successfully treated with a second penile preserving procedure, including partial penectomy, and remain disease free at 32.5 mos follow-up. Overall, these data support the role of OSS as a safe option for selected patients with low risk primary tumors (Tis, Ta, T1a, 65% of our OSS cohort) and even select high risk penile tumors (i.e., T1b-T2, 35% of our OSS cohort) involving the shaft skin and distal glans penis.

The majority (88%) of patients in this series presented with a LR within 5 years of treatment, and only 59% presented within 2 years of undergoing OSS. This is consistent with previous series, which report that the majority of LRs are identified within 5 years of diagnosis [5,8,22]. Among the subset of patients with a median follow-up of 73 months the incidence of LR increased to almost 23% providing the rationale for follow-up beyond 5 years. Together, these data emphasize the importance of stringent surveillance in patients undergoing OSS for a minimum of 5 years with consideration for longer follow up given the risk of late recurrence.

We found that use of laser therapy compared to excisional treatment for pTa/pT1a disease was associated with worse local RFS. In their series of 29 patients, Frimberger et al [23] treated 12 patients with T1 and T2 disease using Nd:YAG laser coagulation. There was only 1 recurrence in the T1 group and none in the T2 group. A different group reported on use of Nd:YAG laser for treatment of 54 patients with penile carcinoma, of which 39 had pT1 or pT2 disease [24]. The LR rate was 42%, which is likely

attributable to longer duration of follow-up, as more than half of patients presented with LR at a time greater than 53 months following treatment. In our series, laser therapy was used either alone or as an intraoperative adjunct to OSS. In cases of combination therapy, frozen sections were obtained, and laser coagulation was utilized in cases where residual noninvasive carcinoma was present to achieve negative margins. Our results suggest that caution is warranted in using this approach with invasive carcinoma. We hypothesize that among tumors where another organ sparing approach was combined with the laser to eradicate residual disease that additional excision (rather than laser) may have resulted in a lower recurrence rate. This however is speculative and remains to be proven.

Our series has several strengths. This is one of the larger prospectively maintained data sets to describe a variety of

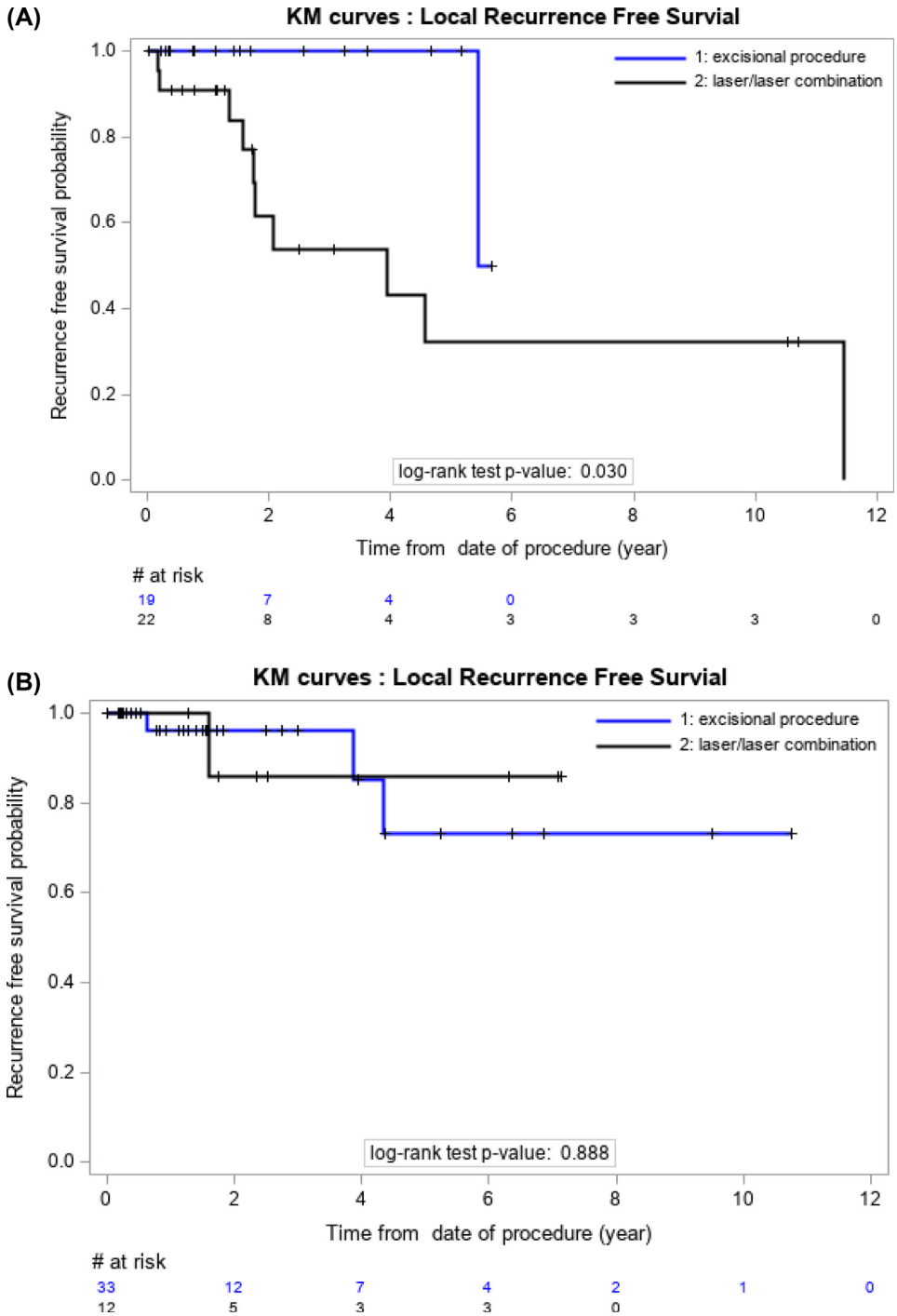

Fig. 3. Local recurrence free survival stratified by type of procedure performed (excisional versus laser) A) pTa/T1a disease, B) ≥pT1b disease C) pTis disease.

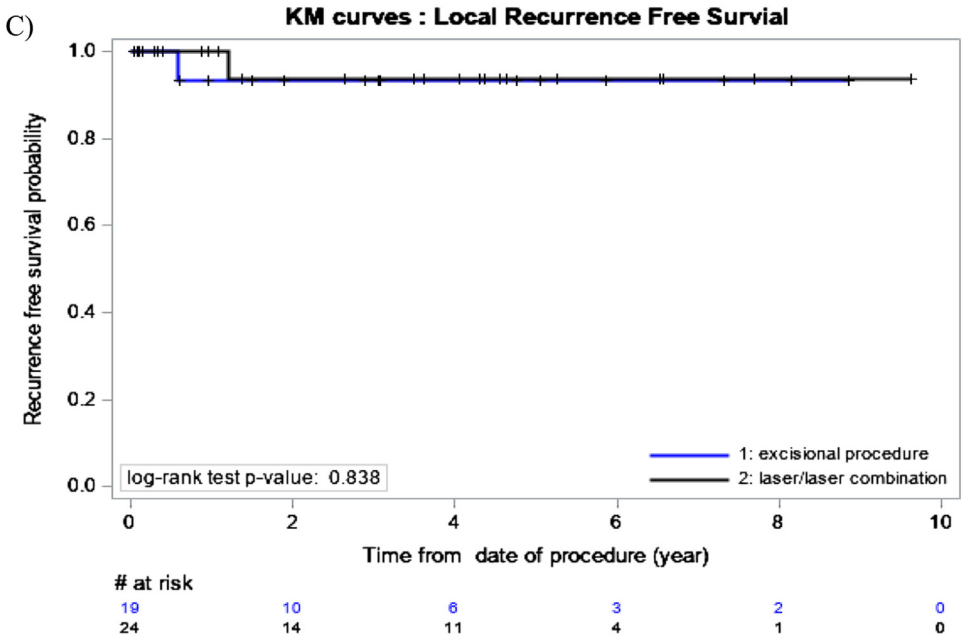

Fig. 3. Continued

organ sparing techniques where virtually all patients had negative surgical margins. While most data was prospectively entered, a portion of the data was retrospectively analyzed, therefore potential for unknown confounders and biases exists. We were unable to obtain information regarding cancer specific survival as the exact cause of death was not ascertained, and retrospective collection was not feasible in many cases. An additional limitation includes lack of comparative data on sexual function before and following OSS, which was not collected in a prospective manner. The prospective series by Yang et al [25] nicely describes maintenance of erectile function and sexual satisfaction when comparing a glans preserving versus a partial penectomy procedure. The number of LR events in the series was small and limited performance of a multivariate analysis. Our data represent the experience of a single tertiary referral center where 97% of procedures were performed by 1 surgeon (CAP). Concerns regarding how these data might compare with a population-based experience could arise. We believe that these considerations are counterbalanced by a consistent treatment approach to achieve negative surgical margins, and prospective data collection for most cases.

Lastly, we do not have information regarding distance from the tumor to the final tumor free margin. The data from Sri et al [15] who retrospectively evaluated this question are noteworthy in that only those patients with a tumor free margin of less than 1mm had a higher local relapse rate. We believe that the use of frozen section analysis is an invaluable tool when performed by dedicated GU pathologists. In our study frozen section analyses for all OSS and partial penectomy cases was performed using the same team of GU pathologists and were reflective of the permanent section in all cases.

Penile cancer is a rare disease where centralization of care should be considered [26]. Data in the present series are certainly consistent with those of Baumgarten et al [20] in the multicenter referral tertiary center experience. Thus, we believe this series serves to strengthen the existing data on feasibility and outcomes of OSS, and further provides guidance on the management of LR.

5. Conclusions

OSS using a variety of techniques to achieve negative surgical margins provides long-term effective local control for localized penile cancer. Most LRs can be successfully treated with further penile preserving strategies with little if any detriment to survival. Long-term follow-up is essential as recurrences have been noted beyond five years. While the use of laser therapy among patients with in situ carcinoma alone was effective, its use among patients with co-existing invasive tumors was associated with higher rates of LR.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2021.02.004.

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