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Penile Superficial Squamous cell Carcinoma (SCC) Submitted to CO_2 Laser Excision only: Oncologic Outcome of T1 Disease in 25 Years-Long Experience

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PENILE SUPERFICIAL SQUAMOUS CELL CARCINOMA (SCC) SUBMITTED TO CO_2 LASER EXCISION ONLY: ONCOLOGIC OUTCOME OF T1 DISEASE IN A 25 YEARS-LONG EXPERIENCE

Clinical pathological evaluations in patients treated with carbon dioxide laser microsurgery

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Abstract

Purpose. We retrospectively identified patients with ascertained T1 SCC pf the penis who were submitted to laser excision only, in order to evaluate clinical and pathological characteristics which can associate with outcomes.

Materials and Methods. Peniscopic magnification and 5% acetic acid application were performed for diagnosis and prior to CO_2 laser excision. Only naïve patients with no urethral (> 5 mm from the meatus) neither shaft lesions were considered. Specimens were all reviewed in order to re-assess pathological characteristics: stage, grade, invasion depth, carcinoma in situ, margins, tumor extension, lymphovascular invasion and HPV infection. Association between local recurrence (LR) and prognostic factors was ascertained with Fisher exact test and Chi-Square test for categorical variables and Wilcoxon rank sum test for continuous variables.

Results. A total of 56 pT1 stage patients were identified. After a median follow-up of 66 months (range: 12-256), 53 patients are alive and disease free, whereas 3 died of unrelated and inter-current diseases. Thirteen (23.21%) had a LR, with 4 suffering multiple recurrences and 1 needing a partial amputation 30 months following primary excision. Only 2 (3.57%) patients had inguinal nodal metastasis in one node. LR had a positive correlation with positive micro-surgical margins (one-sided Fisher p value .0019) and depth of invasion and a negative correlation with tumor extension (one-sided Wilcoxon p value of .0028 and .0054, respectively). A logistic regression model included margin status, depth of invasion, tumor extension and presence of CIS as significant variables.

Conclusions. CO_2 laser excision of selected pT1 SCC of the penis is a highly reliable procedure which associates with excellent oncological and organ-sparing long term results. Predictive variables can be identified and a model that estimates the risk of this event could be adopted.

Keywords: penile neoplasms, lasers, p T1

INTRODUCTION

Squamous cell carcinoma (SCC) of the penis is a rare tumor. Incidence ranges from 0.1 to 0.9/100.000 men in western countries. Traditional treatment of primary SCC of the penis consists of a total or a partial amputation performed at 1.5-2 cm from the tumor border. Superficial location of many small lesions promoted conservative procedures, as local excision and laser surgery. These techniques represent an effective alternative to demolitive surgery specially in superficially T1 cancers [1-3]. In our Institution, an alternative microsurgical CO_2 laser excision has been introduced in the treatment of superficial penis carcinomas since 1982, aiming at achieving a surgical conservative management for lesions of any surface extension, maintaining adequacy of the excision and obtaining adequate surgical specimens for histology. This microsurgical method is performed in One Day Surgery setting using a magnification lens and permits a safe, precise and complete excision of early penile lesions, also those involving the whole glans surface with minimal blood loss. Initial functional and oncologic outcomes were excellent [4]. The main limitations of this procedure are the minimal penetration depth of CO_2 laser, able to remove tissue up to 2 or 3 mm according to site, and the inadequate bleeding control in spongious corpora, where the excision could be inaccurate. Hence, the standardized indications are in situ and initially invasive penile carcinomas, no deeper than 2-3 mm.

This study analyzes long term incidence of local and nodal recurrences, global outcome and definitive success of organ preservation in 56 naïve patients primarily submitted to laser CO_2 conservative surgery for a pT1 cN0 SCC of the penis, in order to investigate pathological variables and the clinical behaviour of the disease at this stage.

MATERIALS AND METHODS

Between 1982 and 2006 included, 224 patients had been submitted to CO_2 laser excision for a superficial SCC of the penis at the Fondazione IRCCS Istituto Nazionale Tumori of Milan, Italy. Clinical and pathological information as well as pathological material have been retrospectively collected from clinical records and pathological reports. All patients of this series have been selected for well defined clinical and pathological features that are reported below.

Clinical evaluation and Surgical procedure. Following full clinical examination and palpation of the groin, a peniscopy was performed before the surgery. Peniscopy consists of a microscopic vision with a lens having a magnification power of 10-20X HPF and 5% acetic acid application, in order to ascertain the diagnosis and define fine details such as surface extension, elevation, number of sites, and borders of planned excision. Primary early tumors were reported as uniformly flat or slightly risen or exophytic lesion of the glans and/or the sulcus. Patients with recurrent lesions, or with an extension along the urethra > cm 0,5 from the meatus, or with tumors involving the penile shaft have not been included in this series. Palpation of the groins was the standard examination for the evaluation of nodal enlargement. None of the patients had palpable inguinal nodes at first diagnosis. Laser CO_2 excision was performed under peniscopic magnification and 5% acid acetic application. First clinical control was planned 1 month after micro-surgery. Follow-up schedule provided clinical examination and peniscopy every 3 months up to 2nd year, every 6 up to 5th year and annually thereafter. Further examinations (abdominal, pelvic and inguinal ultrasound or CT scans) were performed only following clinical indications.

Pathological examination. All histological slides (laser and further penectomy samples) have been reviewed in order to re-assess some variables: pT stage, histologic grading, invasion depth, presence of intraepithelial carcinoma, tumor extension, and involvement of the margins (see below). The 2002 American Joint Committee on Cancer TNM staging system has been used for pathological staging [5] and all the tumors have been categorized as pT1 accordingly. Histological grade has been classified as poorly, moderately and well differentiated [6] . Primary lesions have been histologically classified as typical SCC or variant SCC of the 2004 WHO histopathological classification system [7]. Depth of invasion has been measured from the squamous epithelium basement membrane to the deepest invasive carcinoma cells. In ulcerated lesions, depth of invasion has been measured from the deepest point of invasion to the surface of the ulcer. Penile high grade squamous intraepithelial neoplasia (PIN), lymphovascular invasion and association with HPV infection have been evaluated. HPV infection has been evaluated by histologic changes due to viral presence as mitotic frequency, nuclear enlargement of the middle layer and keratinization disturbances. Table 1 summarizes the main histopathological features of the primary tumourtumor.

Statistical analysis. Statistical tests have been carried out to ascertain the presence of an association between local tumor recurrence and the available prognostic factors. In particular,

Fisher Exact Test and Chi-squared Test [8] have been used for studying association between local tumor recurrence and the following factors: microscopic tumor positive margin, intraepithelial carcinoma, HPV infection, and tumor grade. Wilcoxon rank sum test [9] has instead been used for testing the difference between the distributions of tumor extension, and of tumor invasion, when local tumor recurrence is present or absent. A logistic regression model [10] has been developed to estimate the probability of local recurrence given the prognostic factors found to be significant. Moreover, the association between HPV infection and tumor grade has been studied by Fisher Exact Test and Chi-squared Test, and the distributions of tumor invasion, stratified for tumor grade, have been analyzed by Wilcoxon rank sum test. Analysis have been carried out using R® software (version 2.4.0).

RESULTS

Among 224 patients submitted to laser excision for a SCC of the penis, 56 were selected for having received surgery only for a pT1 disease. Patients' median age was 61 years (range 32-82) (Table 1). After a median follow-up 66 months (range 12-256 months 3 patients died of unrelated and inter-current diseases, whilst 53 patients are alive and free of disease. No patient was lost to follow-up. Thirteen patients (23,21%) had local recurrences. Four patients had more than one recurrence. One of them had a local recurrence in the sulcus, months after first excision, and he was re-treated with a new laser treatment. Unfortunately, follow-up visit was delayed and the patient suffered a further recurrence 30 months after first excision and a partial amputation of the penis was necessary to remove a grade 2 pT3 tumor. Neither local recurrence nor nodal metastasis have been recorded since then, and the patient is alive and free of disease 36 months after partial amputation. Three further patients suffered a local recurrence, 20, 22 and 55 months following primary excision that could be successfully treated with a new laser excision, but developed an unilateral lymph-node enlargement which needed an inguino-crural lymph-node dissection. Nodal metastasis in one node was found in 1 only of these 3 patients, and no adjuvant chemotherapy was delivered. All three are alive and free of disease, 24, 48 and 60 months after lymphadenectomy. One further patient had unilateral inguinal enlargement 7 months after laser excision with no local recurrence. Subsequent inguinal lymphadenectomy revealed metastasis from SCC in one inguinal node. No adjuvant chemotherapy was delivered and the patient remains alive and free of disease 62 months after inguinal surgery. So far, only two patients (3.57%) had ascertained inguinal nodal metastases. As reported above, one patient

developed a nodal metastasis following just one laser excision of a microinvasive (mm 1.1) grade 2 negative margins tumor, and one developed a nodal metastasis following 2 local recurrences, having a primary invasive (mm 1.1) grade 2 tumor. Such a low rate of nodal metastases prevents any reasonable statistical evaluation of this risk.

No major complications requiring surgical or endoscopic procedures occurred. In particular no significant meatal or urethral stenosis became evident during follow-up.

Evaluation of sexual function following CO_2 laser excision is not reported in this paper that aims at evaluating oncological efficacy and safety of this procedure. This important evaluation for a conservative technique is planned for the whole series of patients who had been submitted to this conservative procedure independently of stage and administration of neoadjuvant and/or adjuvant chemotherapy.

Risk factors analysis

There is a strong positive association between tumor local recurrence and involvement of margins (one-sided Fisher p-value = 0.0019 and Chi-squared p-value = 0.0046). After grouping patients according to presence or absence of intraepithelial carcinoma, the association between tumor local recurrence and involvement of margins remains significant for the group of patients having intraepithelial carcinoma (one-sided Fisher p-value = 0.0202 and Chi-squared p-value = 0.0446), whereas it looses significance in the other group (one-sided Fisher p-value = 0.0833 and Chi-squared p-value = 0.1649).

There is a strong positive association between local recurrence and tumor invasion; the distribution of tumor invasion for those patients who had local recurrences is stochastically higher than the distribution for those who had not (one-sided Wilcoxon p-value = 0.0028). (Figure 1).

There is a strong negative association between local recurrence and tumor extension; the distribution of tumor extension for those patients who had local recurrences is stochastically lower than the distribution for those who had not (one-sided Wilcoxon p-value = 0.0054). (Figure 1).

There is no significant association between tumor local recurrence and other factors such as presence of intraepithelial carcinoma (one-sided Fisher p-value = 0.1402 and Chi-squared p-

value =0.2801), HPV infection (one-sided Fisher p-value = 0.2295 and Chi-squared p-value = 0.4669), and tumor grade (one-sided Fisher p-value = 0.6112 and Chi-squared p-value = 0.7586).

The results of these tests are shown in the table 2.

In the light of these results, we developed a logistic regression model without interactions to understand the joint role of the significant prognostic factors in explaining local recurrence, and to estimate its probability p. Factors considered in the model are involvement of margins (Margins = 1 if positive, = 0 if negative), tumor extension and invasion (in mm); presence of intraepithelial carcinoma (CIS= 1 if present, = 0 if absent) has also been included because of its effects on the association between margins status and local recurrence. The overall fitted model is:

$$\log\left(\frac{p}{1-p}\right) = -1.715 + 1.638 * CIS + 1.939 * Margins + 1.519 * Invasion - 1.016 * \log(Extension)$$

with Akaike's AIC equal to 50.982. See Figure 2. Even if the other variables (HPV infection, tumor grade, and patient age) are included in the model, these are discarded by forward/backward stepwise algorithms[10] for model selection based on Akaike's AIC (full model's Akaike's AIC= 53.73).

Finally, there is no significant association between HPV infection and tumor grade (two-sided Fisher p-value = 0.1851 and Chi-squared p-value = 0.2635), and there is no significant difference between the distributions of tumor invasion for tumors with low grade (grade 1) and tumors with high grades (graded 2 or 3) (one-side Wilcoxon p-value = 0.1135).

DISCUSSION

Microsurgical CO_2 laser excision was introduced in our institution since 1982, as an alternative treatment of selected superficial penile carcinomas. This series include very selected patients with superficial lesions who had been considered suitable for laser excision and who were not submitted to any therapy prior to laser. Our standardised indication of CO_2 laser microsurgical method under microscopic vision is the conservative excision of the in situ and initially invasive penile carcinoma, with a vertical extension no greater than 2-3 mm., as the laser excision depth ranges from 1.5 to 3 mm, which is based on the thickness of the lamina propria following the curvature of the glans and coronal sulcus (Figure 3). As a consequence of these

selective criteria, 13 local recurrences and 2 nodal metastases only were experienced in our series. Only one patient required a partial amputation and no unfavourable outcome was recorded. Rate of local recurrences (23%) in the present series is comparable with data from Windahl and Anderson [8] and from Lont [3] that reported local recurrences in 19% and 25% following Nd:YAG laser and CO_2 laser excision, respectively. On the other hand, Meijer [12] recently reported as many as 12 (57%) local recurrences among 21 T1 SCC submitted to Nd:YAG laser excision.

Evaluation of risk factors for local recurrence in our series is reported in table 2; considering each factor separately, those significantly associated to tumor local recurrence are margins status, depth of invasion and tumor extension. A multivariate analysis, by means of a logistic regression model, confirms that margins status, presence of intraepithelial carcinoma depth of invasion, and tumor extension are jointly significant prognostic factors of local recurrence.

The intuitive fact that margin status is particularly relevant in the evaluation of local recurrence risk is thus confirmed by the analysis. Lont [3], who examined, by Cox regression analysis, the influence on local recurrence of clinical T stage, tumor grade, infiltration depth, lymphovascular invasion and complete tumoral excision, found that only positive surgical margin was an independent prognostic factor.

Depth of invasion deserves a special interest from anatomical and staging points of view. Sub epithelial layer which invasion defines pT1 tumors is the prolongation of the foreskin lamina propria and separates the corpus spongiosum from the glans epithelium without any transition so that the lamina propria adheres firmly to the underlying corpus spongiosum. The thickness varies from 1 mm at the glans corona to 2.5-3 mm near the meatus [9]. The transition between corpus spongiosum and lamina propria can be difficult to determine, with important consequences in terms of correct staging allocation. The tumor local recurrence in 7 out of 8 patients with CIS in adjacent epithelium suggests that genetic mutations can already be present in the tissue near the invasive tumor without appreciable alterations.

The fact that tumour extension has a negative correlation with local recurrence risk might seem unclear. This could be explained by the different approach used to deal with superficially broader tumours. Indeed, larger lesions need to be treated with a wider excision than smaller ones: when the lesion was less than 20 mm in diameter a primary laser excisional biopsy was done, whereas for larger lesions a partial or total surface laser excision was performed; in

particular, total surface excision was carried out for lesions extending more than half the circumference of the organ (> 30 mm). On the other hand, this phenomenon could be just a consequence of patients' selection bias, since broader lesions may be less aggressive than smaller ones, as the latters could inlcude early stages of intrinsically aggressive cancers.

Figure 2 illustrates a logistic model that could help in estimating risk of local recurrence for each patient. Patients having an elevated risk of local recurrence (probability > 0.5) could be considered for an early re-treatment. Taken as a category, this includes patients with positive margin status, intraepithelial carcinoma, depth of invasion > 1 mm and tumor extension < mm 20. On the other hand, patients with features associated to a lower risk could be only monitored.

In our series, inguinal metastases were a rare event (3.6%), and this prevents any analysis of risk. Just one of these nodal metastases occurred among patients with recurrent local disease. The prognosis of SCC largely depends on the stage: pathologic findings related to the prognosis are the site of the primary, histologic type, grade, depth of invasion and vascular invasion. Few series have reported patients with superficial carcinomas with a long term clinical observation: the involvement of lamina propria in pT1 penile cancers has been reported in many series with differences in lymphnode metastatic rates ranging from 0% as far to 58,3% [3,8, 10-15]. Explanations for these heterogeneous findings may be the different criteria used for tumor staging, difficulties in measuring tumor invasion which can relate with inaccuracy of the measurement of lesions with peculiar pathological features, different tecniques of surgical excision, small number of patients in the series and a selection bias as well. Among the factors predictive of lymphnode metastasis the depth of invasion has been established as one of the best predictor. Different cut-off of depth invasion, ranging from 1 to 6 mm, aiming at predicting nodal metastases have been proposed. In our series of nodal metastases occurred in 2 patients only, and both had a depth of invasion greater than 1 mm, but further contributions are needed to confirm that < 1 mm thick pT1 tumors are not associated with the risk of nodal metastases.

Detailed evaluation of functional results and of complications following CO_2 laser excision is not within the aims of this study. For instance, no major complications requiring further operative procedures occurred in this series. Sexual function outcome, which is of outstanding importance following a conservative procedure, is going to be evaluated in the whole series of patients submitted to CO_2 laser excision for any superficial stage and in multimodality setting (e.g. those patients who received chemotherapy).

CONCLUSIONS

In this retrospective series of selected pT1 penile SCC patients submitted to CO_2 laser excision, both oncological and organ-sparing results are excellent: disease specific survival is 100% as 3 patients died of unrelated causes and only one patient needed a partial amputation. Nodal metastases were a rare event while local recurrences were in a range reported by other series. This latter event has been analysed in order to identify predictive factors. Positive correlation with margin status, depth of invasion, presence of CIS and negative correlation with extension of disease were ascertained with a logistic regression model. An early re-treatment could be suggested in clinical setting for patients having elevated risk of local recurrence according to the model.

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Table 1. Summary statistics of some clinical, anatomical and pathological characteristics

Pt. age	
Min	32
Max	82
Av	59.9
Histological grade	
G1	40 (71,4%)
G2	14 (25,0%)
G3	2 (3,6%)
Regional lymphnode metastasis	
Yes	2 (3,6%)
No	54 (96,4%)
Carcinoma in situ (CIS)	
Yes	25 (44,6%)
No	31 (55,4%)
HPV	
Yes	15 (26,7%)
No	41 (73,2%)
Mean invasion depth (mm)	
Min	0.12
Max	2.50
Av	0.60
Extension (mm)	
Min	3
Max	99
Av	20

Table 2. Association between local tumoral recurrence and prognostic factors.

Association with local tumor recurrence	p-value	Significant association
Margins	0.0019 (one-sided Fisher test)	Yes
Margins when CIS present	0.0202 (one-sided Fisher test)	Yes
Margins when CIS absent	0.0833 (one-sided Fisher test)	No
CIS	0.1402 (one-sided Fisher test)	No
HPV infection	0.2295 (one-sided Fisher test)	No
Tumor grade	0.6112 (one-sided Fisher test)	No
Tumor extension	0.0054 (one-sided Wilcoxon test)	Yes
Tumor invasion	0.0028 (one-sided Wilcoxon test)	Yes

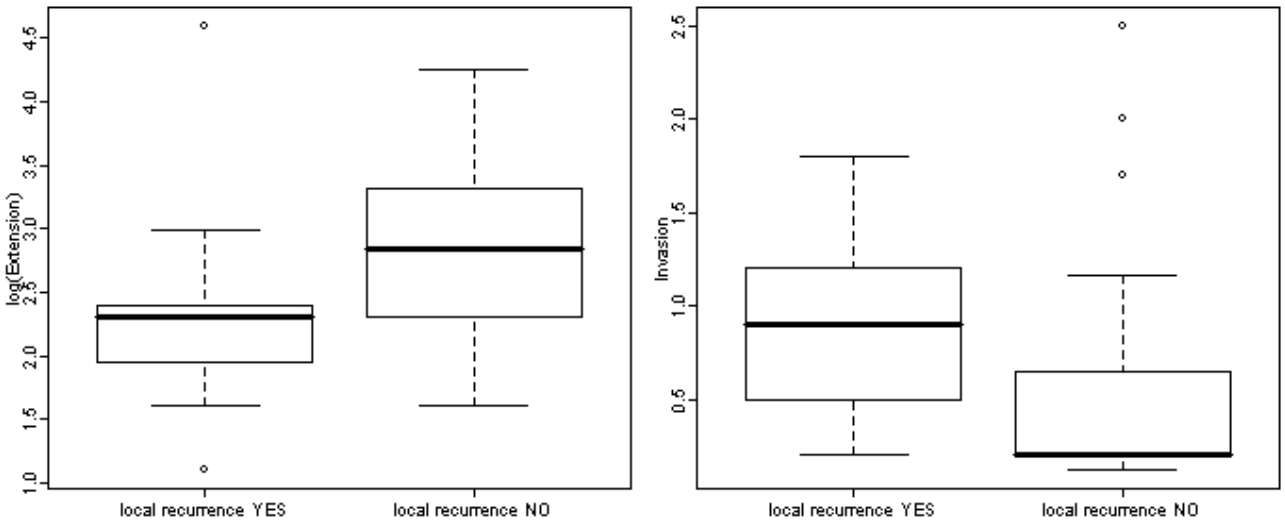

Figure 1. Left: box-plots of the logarithm of tumor extension stratified for local recurrence. Right: box-plots of tumor invasion stratified for local recurrence.

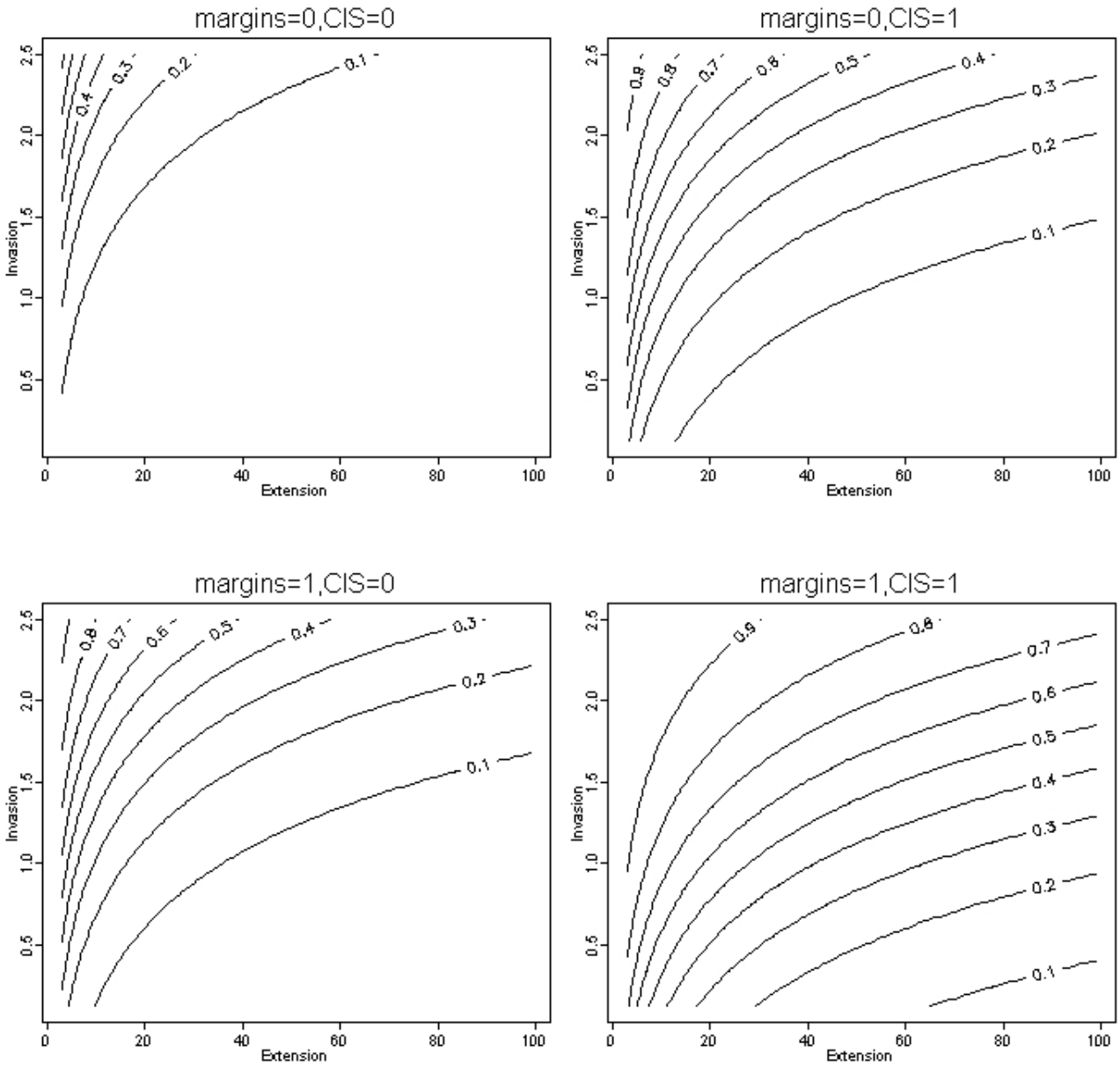

Figure 2. Estimated probability of local recurrence as a function of extension and invasion, in the 4 scenarios corresponding to presence/absence of intraepithelial carcinoma and presence/absence of microscopic tumor positive margin.

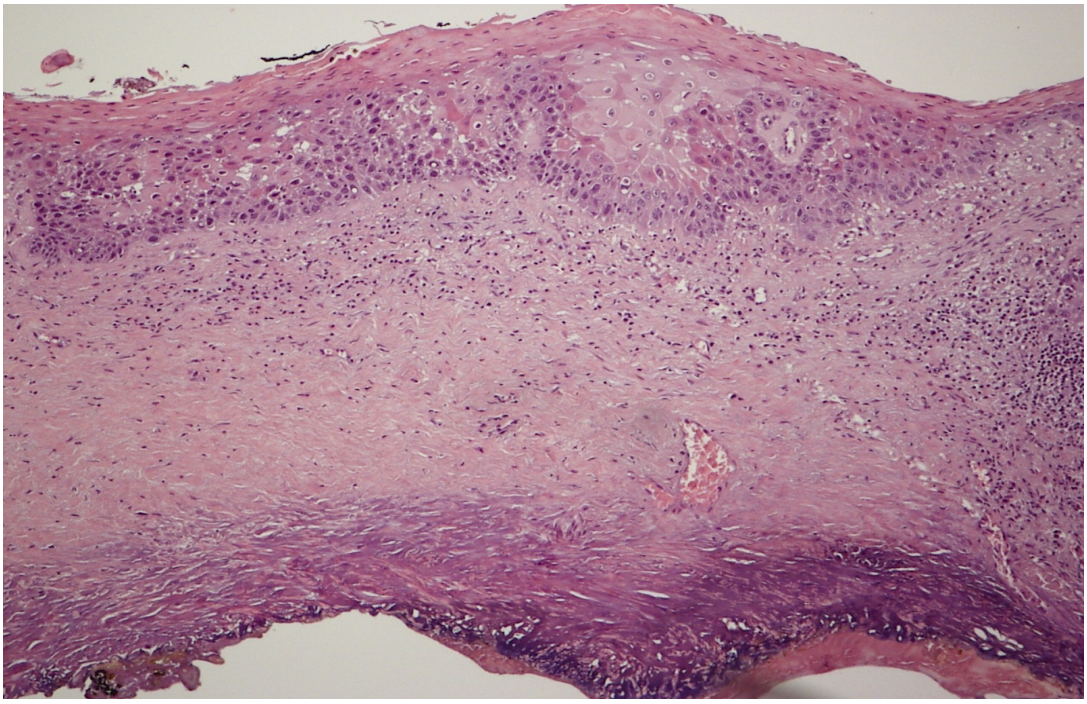

Figure 3. Microscopic vision of a CO_2 laser biopsy: the laser excision depth from the superficial epithelium of the glans to the margin is 2-3 mm.

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