Title

Frozen section analysis for organ-conserving surgery in penile cancer: assessing oncological outcomes and trends of local recurrence.

Authors

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Abstract

Introduction and Objectives:

The local recurrence rate of penile cancer following surgical excision is reported in many series to be between 6 and 29%. Intra-operative Frozen Section (FS) is a useful tool to ensure safe microscopic margins in organ sparing procedures in penile cancer. In this series, we assessed the rates of positive margins and patterns of local recurrence in a multi-centre cohort of patients undergoing penile preserving surgery assisted by intraoperative FS analysis.

Materials and Methods:

We reviewed all those patients for whom intra-operative FS was employed during penile preserving surgery in three tertiary referral centres between 2003 and 2016. We assessed whether the use of FS altered the surgical technique and what affect it had on positive margins and recurrence rates.

Results:

169 patients were identified. Of these, intra-operative FS examination of the surgical margin was positive in 21 (12%) cases. Final histological examination confirmed cancer-free margins in all but one patient (99.4%). Overall, 9 patients developed local recurrence (5.3%).

Conclusions:

In this series, intra-operative FS contributed to a very low rate (5.3%) of local recurrence. We noted an extremely low positive margin rate (0.6%) which highlights the benefit of incorporating FS analysis into organ preserving surgery for penile cancer.

Main text

Introduction:

Squamous cell carcinoma (SCC) is the most common type of penile cancer (>95%).[1] The majority of tumours occur on the distal penis, involving the glans, foreskin or coronal sulcus.[2,3] Radical surgery with partial or total penectomy provides excellent local control but is associated with a significant impairment of sexual function and often results in difficulty or inability to void whilst standing.[4] It is also associated with significant psychosexual trauma in more than 50% of patients.[5] Although radiotherapy offers organ preservation there is a high incidence of local recurrence of around 45% with frequent local complications which include skin necrosis, meatal stenosis, urethral fistula, chronic oedema and penile pain.[6] Furthermore, radiation-associated changes make it more difficult to diagnose local recurrence of penile cancer.[7-9] Surgery is therefore the treatment of choice for the primary lesion. Organ sparing operations, such as partial glansectomy and glansectomy with or without skin grafting (SSG) have emerged as viable procedures with comparable oncological outcomes and better functional results than traditional partial or total penectomy.[10-12]

Reported local recurrence rates of penile cancer range from 6 to 29%, the majority recurring within the first 2 years. For this reason, EUA guidelines currently recommend follow-up for local cancer recurrence every three months for the first two years and then six-monthly until at least five years postoperatively.[13] It has been theorised that the mechanisms for local cancer recurrence may be related to inadequate primary surgical resection, a development of a 'new' primary cancer due to underlying skin changes predisposing to neoplasia, or an increased malignant potential of the cancer on a histological level; which may include subtypes of SCC such as basaloid or concurrent lymphovascular invasion.[14] Surgical margin assessment is therefore mandated in conservative penile cancer resections.[13] Intra-operative frozen section

(FS) pathology review provides the operating surgeon with 'real-time' information to allow adaptation of the surgical procedure being undertaken. This approach has the potential to avoid positive margins and reduce the need for repeat surgery to achieve clearance of the primary lesion at a later date. It is important that the resected specimen is carefully orientated and clearly presented to the pathologist so that a definitive statement can be made with regard to skin, urethral and corporal or deep margins.

Aims:

To describe our technique and experience with the use of intra-operative FS in penile-conserving cancer surgery and to assess our rates of negative surgical margins in penile preserving surgery and its impact upon local recurrence rates.

Materials and methods:

This study assessed patient data collected from three supra-regional referral centres for penile cancer in the United Kingdom (UK), providing treatment for a population of approximately 9 million patients. Each site undertakes regular penile cancer multi-disciplinary team (MDT) meetings and independently compiles a database of all penile cancer patients undergoing treatment.[15] These databases were interrogated to identify all patients who had undergone penile-conserving surgery with intraoperative FS analysis. Data collection was performed up to July 2016. This date was selected to ensure that all patients had a minimum of two year follow up postoperatively, as this is the time when local recurrence is thought to be most likely to occur. Although all patients had undergone surgery over 2 years previously, not all had been reviewed recently by a penile-cancer surgeon. Therefore, if patients had at least 6 months confirmed specialist follow-up, they were included for analysis.

Between January 2007 and July 2016, 169 patients were identified who met the criteria above. These patients had a prior histopathological diagnosis of penile cancer. Depending upon the pre-operative clinical and radiological findings patients were offered local excision, glansectomy (with or without glans reconstruction using SSG) or partial penectomy. FS examination was performed in those cases where preservation of the greatest possible length of penis was requested and achievable oncologically and functionally - especially important in those, often younger, patients who were particularly keen to maintain a standing void or retain penetrative ability.

Four consultant urologists performed the procedures across three sites. A standardised surgical technique was performed according to the procedure undertaken. For glansectomy procedures, dissection was performed above the level of Buck's fascia. Once local excision was considered by the operating surgeon to be macroscopically and clinically complete, biopsies were taken from the corporal bodies underlying the base of the lesion; this represented the deep resection margin. A separate complete circumferential urethral biopsy – the "urethral donut" was taken in glansectomy and partial penectomy procedures. In some cases, a separate skin margin was taken. These specimens were then sent for FS assessment. Depending upon the centre of treatment, the reporting histopathologist was either present in the operating theatre, the surgeon took the specimen to the histopathology lab personally, or discussion with the operating surgeon took place pre-operatively to ensure a clear orientation of the specimen for FS. Either one or two pathologists with a special interest in penile malignancy reviewed the frozen sections at each site and results were given directly to the operating surgeon either personally or by telephone. The time taken for frozen section analysis was not always documented, but anecdotally is between 30 – 40 minutes. In cases of positive FS, further resection was performed under the same anaesthetic until negative FS margins were achieved. All tissue used

for FS was subsequently subjected to formal routine paraffin-based analysis to ensure that the quality of FS reporting was assured. It was not always specified retrospectively whether a positive FS referred to *carcinoma-in-situ* or invasive malignancy. For this reason, any positive finding on FS analysis was recorded as positive in our results. However, only invasive malignancy was considered recurrent disease. All patients were followed up in the outpatient clinic in line with EAU guidelines for signs of recurrent disease and to assess functional results.[13]

Results:

Over a period of 9 years (January 2007 to July 2016), 169 patients had intra-operative FS samples taken during penile-preserving surgery to assess resected margins. The mean age of this population was 62 years (range: 31- 95years). Median follow-up was 45 months (range: 6-170 months). Of these 169 patients, 77 (45.6%) had a partial penectomy, 70 (41.4%) a total glansectomy, 9 (5.3%) a wide local excision, 8 (4.7%) a glans resurfacing, and 6 (3.6%) a partial glansectomy.

Twenty-one patients (12%) had a positive margin on initial FS, which mandated further tissue resection during the same operation, and a repeat FS to confirm clearance. All but one patient who initially had positive FS and then subsequent negative FS, were found to have cancer-free surgical margins on the final paraffin based histopathological reports (99.4%). One patient showed extensive inflammation with non-conclusive FS findings but he had a negative margin on the final paraffin based report. Overall, 9 patients (5.3%) developed a local recurrence. Median time to recurrence was 10 months (Range 3 - 42). The characteristics of these patients are identified in table 1 below. The histology, final pathological staging and grading for the group are summarised in tables 2 – 4.

Discussion:

Historically, penile cancers were excised with at least a 2-cm margin from the tumour edge.[17, 18] To achieve this, considerable penile length had to be sacrificed and the consequence of this was more profound in patients with a shorter pre-operative penile length. This traditional concept of surgical margin excision has been challenged by Minhas et al.,[19] as most penile lesions tend to occur distally meaning most can be treated with penile-sparing surgical techniques. Preservation of penile length reduces the negative functional and psychosexual effects in penile cancer patients, but the presence of positive resection margins results in an increased incidence of local recurrence and re-operation. There is also evidence in the literature that insufficient local treatment can also influence development of lymphatic metastasis and disease progression.[20] In the study by Minhas et al, 51 patients underwent penile-conserving surgery (wide local excision, partial or complete glansectomy, or partial penectomy with SSG). They used intraoperative FS analysis in only selected patients when there was a suspicion of tumour involvement at the excision margin. Men with positive margins received further local surgery to complete tumour clearance. In that study 6% patients had a positive surgical margin and required further surgery. At a median follow-up of 26 months, 4% patients had developed local tumour recurrence.[19]

The pathological assessment of surgical margins is essential in cancer surgery since tumour-positive margins increases the risk of local recurrence. Up to 9.5% of general surgical tumour specimens thought to be clinically negative are subsequently found to have positive surgical margins.[19] The adoption of intra-operative FS allows this error margin to be significantly reduced but accuracy does depend on the type of tissue being resected and how the margins are processed and reported. Several recent retrospective reviews have concluded an overall efficacy of 95% with the use of FS.[21-23] Furthermore, a more recent systematic review of the use of organ sparing surgery in penile cancer has recommended the use of FS analysis

intraoperatively.[25] For the best results, it is important that the pathologist and operating surgeon work closely as a team, preferably in the operating theatre, so that the most appropriate biopsies can be taken and be accurately orientated to provide the specific answers required by the operating surgeon.

With the adoption of intraoperative FS in these penile resection surgical techniques, the incidence of a positive margin is greatly reduced, saving patients the need for a further operation and the distress this causes, whilst also improving oncological outcomes. In our study of 169 patients managed by surgical resection with intra-operative FS, we observed a low (5.3%) rate of local recurrence. It is of interest that every patient who had a local recurrence had primary disease of at least grade 2. The relatively high rate of initial positive FS (12%) samples in our series reflects our aim for maximal penile preservation when specifically indicated in those (often younger) men to whom residual function and cosmesis is paramount. Although all macroscopic disease is resected with a visible clear margin, confidence in the technique incorporating FS analysis allows narrower surgical margins to be attempted. It highlights the benefit of integrating FS analysis into the management of all penile-conserving procedures that we noted an extremely low (0.6%) positive margin rate. This rate may be compared to a recently published paper by Sri et al. (2018) demonstrating a positive margin rate of 7.6% when FS analysis was not routinely employed[23].

It is important to note that lymph node disease and metastases were not assessed during this study and therefore rates of such cannot be commented on. Furthermore, the TNM staging documented is the 2010 TNM staging, rather than the updated 2018 system.[16] This was the staging system in use at the time of surgery for all patients and data were not always available to update patient staging to the current TNM system. Moreover, all data was collected in a retrospective fashion given the relatively small numbers of cases. This is a limitation of most studies analysing penile cancer outcomes and would be best addressed by a larger collaborative

prospective study. All histopathological review was undertaken by pathologists experienced in penile malignancy and subsequently discussed in a multidisciplinary setting. This ensured that results were reported to a confirmed quality and objective standards.

In other studies, local recurrence following partial penectomy is not uncommon; an explanation for this other than an insufficient surgical margin is lacking. In a study by Velazquez et al, involving 18 partial penectomy specimens, positive resection margin was present in 17.5% of all specimens.[26] They found that penile fascia surrounding the urethra and surrounding tissue was most commonly involved, followed by urethral epithelium and lamina propria. Less usual sites included penile skin and corpus cavernosum. The infrequent involvement of corpus cavernosum may be explained by the presence of the tunica albuginea, which offers a substantial physical barrier to tumour spread.[23] This physical barrier effect explains the reasoning behind the change in TNM staging used for penile cancer. The current staging reflects the fact that corporal involvement results in poorer outcomes and therefore is now defined as T3 disease. Chaux and colleagues hypothesise that higher-grade disease or certain histological subtypes may predispose patients to recurrence.[14] This finding was somewhat mirrored by our data, as no patients with grade 1 disease recurred and there was evidence of either aggressive histological subtypes, lymphovascular or perineural invasion in the histology of 3 of our 9 patients (33.3%) who developed local recurrence. A recent study by Sri et al. has demonstrated that recurrence patterns following organ-sparing surgery may be related to embolic events or development of a new primary cancer.[23] However, the numbers of recurrences in our cohort were not large enough to provide statistical support of this theory.

Conclusions:

In our cohort, the local recurrence rate was 5.3% and the positive margin rate was 0.6%. This is lower than many of the rates reported in the literature to date, and we believe that this shows the importance of intraoperative frozen section and advocate its use as an integral part of organ-preserving penile cancer surgery. These results confirm that conservative surgery, when judiciously combined with careful frozen section analysis is a safe, effective and oncologically sound technique to employ in patients actively seeking maximal organ preservation - both for functional and psychological reasons.

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