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The role of frozen section examination during inguinal exploration in men with inconclusive testicular tumors: a systematic review and meta-analysis

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Abstract: For inconclusive testicular tumors with negative tumor markers, frozen section examination (FSE) during inguinal exploration is recommended. However, FSE is time-consuming and therefore often not requested. Furthermore, the exact diagnostic benefit remains poorly defined. We performed a systematic review and meta-analysis summarizing 12 published studies and our own series of FSE in patients with inconclusive testicular tumors, resulting in a cohort of 1052 FSEs. FSE showed sensitivity of 99% and specificity of 96% with a positive predictive value of 98% and a negative predictive value of 97%. Most importantly, one-third of all testicular tumors investigated were correctly identified as being suitable for testis-sparing surgery and orchiectomy could be avoided. For patients with inconclusive testicular tumors, FSE is useful for deciding whether testis-sparing surgery is an option or whether radical orchiectomy should be performed. Thus, these patients should be optimally treated in institutions where FSE is available. **PATIENT SUMMARY:** We found that intraoperative examination of a frozen section is useful in deciding on whether the entire or only parts of the testicle can be removed. We conclude that frozen section examination should be offered to men with small testicular lesions and negative tumor markers.

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The role of frozen section examination (FSE) during inguinal exploration in men with inconclusive testicular tumors, a systematic review and meta-analysis

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Abstract

For inconclusive testicular tumors with negative tumor markers, frozen section examination (FSE) during inguinal exploration is recommended. However, FSE is time consuming and therefore often not requested. Furthermore, the exact diagnostic benefit remains poorly defined. We performed a systematic review and meta-analysis summarizing 12 published and our own series of FSE in patients with inconclusive testicular tumors resulting in a cohort of 1052 FSEs. FSE showed a sensitivity of 99%, specificity of 96% with a positive predictive value of 98% and a negative predictive value of 97%. Most importantly, one third of all investigated testicular tumors have been correctly identified being suitable for testis sparing surgery and orchiectomy could be avoided.

In patients with inconclusive testicular tumors FSE is useful to decide whether testis sparing surgery is an option or whether radical orchiectomy should be performed. Thus, these patients should optimally be treated in institutions where FSE is available.

Patient summary We found that intraoperative frozen section examination is useful to decide whether the entire or only parts of the testicle can be removed. We conclude that frozen section examination should be offered to men with small testicular lesions and negative tumor markers.

Keywords: testicular germ cell tumor; frozen section

Introduction

Germ cell tumors (GCT) represent the most common tumors of the testis. However, several other malignant (e.g. lymphoma or sarcoma) or benign tumors (e.g. epidermoid cysts, fibrothecoma, post-traumatic hematoma / scar tissue) can also be found on final histopathology. Radical orchiectomy represents the standard of care for malignant tumors. However, in small, resectable benign tumors testis sparing surgery (TSS) is often feasible and can result in significant sparing of healthy functional testicular tissue. TSS therefore reduces the risk of postoperative infertility and hypogonadism and can preserve cosmetic and psychological well-being¹⁻³. Additionally, emerging data suggests that TSS is oncologically safe in selected testicular tumors such as Leydig⁴ and Sertoli cell tumors⁵.

Although preoperative risk factors such as tumor volume, symptom duration, fertility disorders, history of cryptorchidism and testosterone levels can predict final histopathology results^{6,7}, all these variables are not accurate enough to decide whether orchiectomy or TSS should be performed. Given the limited discriminatory value of those preoperative risk factors, the current European Association of Urology guidelines recommend to perform FSE in patients with inconclusive testicular lesions⁸. However, FSE requires not only the instant availability of a specialist pathologist but is also time consuming and therefore often not requested by urologists. Furthermore, the true diagnostic value of FSE remains poorly defined. The aim of this review was to assess the diagnostic value of FSE during inguinal exploration for inconclusive testicular lesions.

Results and Discussion

We identified 12 studies (including 843 patients) eligible for inclusion in the individual patient data meta-analysis (Table 1, Supplementary file 1). The median patient number in the included studies was 30 (range 7-345 patients). Additionally, we included our institutional cohort of 209 patients resulting in a total of 1052 patients for FSE analysis.

Of 1052 testicular tumors, 705 (67%) were correctly identified on FSE as a malignant tumor requiring orchiectomy (Table 1). In contrast, 326 (31%) testicular tumors were correctly identified to be suitable for TSS. Only 9 malignant tumors (<1%) were falsely diagnosed as benign on FSE and required completion orchiectomy later on. These results lead to a sensitivity of 99% (95% confidence interval (CI) 98-99%), specificity of 96% (95% CI 94-98%) with a positive predictive value of 98% (95% CI 97-99%) and a negative predictive value of 97% (95% CI 95-99%). Across all included series FSE showed comparable sensitivity and specificity (Table 1).

Our analysis revealed that FSE represents a valuable and reliable intraoperative decision aid for patients with inconclusive testicular lesions. FSE is particularly helpful in patients with negative GCT tumor markers and small testicular tumors that can be enucleated. In contrast, immediate radical orchiectomy without FSE should be performed in patients with (1) elevated tumor markers or (2) involvement of a substantial part of the testicle (e.g. larger than 2-3cm). To avoid false negative results, we recommend complete enucleation of any suspicious testicular tissue rather than a strategy involving incomplete random sampling. Incomplete resection can also impede follow-up with ultrasonography. Additionally, we also recommend to perform two ipsilateral biopsies of normal testicular tissue to be sent for regular immunohistochemistry. This allows to identify Germ cell neoplasia in situ (GCNIS) which helps to differentiate between epidermoid cysts (GCNIS-neg.) and teratoma (GCNIS-pos.).

Critics of FSE often argue that (1) subsequent histopathology is not possible after FSE and (2) that patients might need to undergo completion orchiectomy in case of false negative FSE results. In our experience, specimens sent for FSE can indeed be used for subsequent regular histopathology including immunohistochemistry, fluorescence in situ hybridization (FISH) or even molecular analyses but pathologists should ideally be informed before that the specimen sent for FSE should also be used for regular histopathology. Completion orchiectomy after false negative FSE was rarely necessary in the current series (<1%). We advise that patients should

always be counseled about the risk of a subsequent completion orchiectomy in case of a differing results between FSE and final histopathology.

Nearly half of all GCT patients do not show serum marker elevation and FSE might therefore be indicated in a substantial proportion of men with testicular lesions. However, if the promising diagnostic accuracy of microRNAs for GCT histology ⁹ are confirmed in commercially available tests, the need for FSE might decrease. Nevertheless, in men testicular lesions and negative classical TM and microRNA, FSE would still be necessary to differentiate other malignant from benign tumors.

In conclusion, FSE shows excellent prediction of the final histology. The use of FSE prevented radical orchiectomy in one third of patients with inconclusive and resectable testicular lesions. Thus, these patients should optimally be treated in institutions where FSE expertise is available.

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