Accuracy and cost of intraoperative lymph node frozen sections at radical prostatectomy

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Abstract

Aim—To assess the value of intraoperative diagnostic examination of frozen sections of lymph nodes removed during radical prostatectomy.

Methods—Pelvic lymph nodes from patients with prostatic carcinoma were obtained (1) as frozen sections during radical prostatectomy, to exclude patients from non-curative surgery, and (2) as paraffin sections postoperatively from lymphadenectomy performed at radical prostatectomy, to stage the tumour and assess need for adjuvant treatment. Findings from the two approaches were used to assess the accuracy and cost of frozen section diagnosis, and to judge the results of omitting intraoperative diagnosis.

Results—In 82 patients frozen section revealed metastasis in six (7.3%), and metastases were found in a further four (4.9%) on paraffin sections (false negatives). Of the 195 patients undergoing staging lymphadenectomy (without frozen section), metastatic cancer was seen in nine cases (4.6%). The frozen section cost of metastatic cancer detection per patient was calculated as £7516 (£550 × 82/6), with an associated false negative rate of 33%.

Conclusions—Frozen section diagnosis of metastatic carcinoma in pelvic lymph nodes before radical prostatectomy has a high false negative rate and is costly. It may not be justified with the observed low incidence of lymph node metastasis.

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Keywords: prostate cancer; frozen section; intraoperative diagnosis

Radical treatment is now offered more often to younger patients with carcinoma of prostate clinically confined to the gland.^{1,2} Pelvic lymphadenectomy remains a routine procedure on undertaking radical prostatectomy. When radical prostatectomy was reintroduced into Britain it was standard practice to perform intraoperative frozen section diagnosis on pelvic lymph nodes to identify the small group of patients with lymph node metastasis, so that unnecessary and inappropriate surgery is avoided. This approach was partly based on the American experience dating back to early 1980s when the incidence of pelvic lymph node metastasis in radical prostatectomy cases was reported to be around 40% for apparently localised disease.³ One of us (EPNO'D) also found in the 1970s that the incidence of lymph

node metastasis in a series of patients with clinically M0 prostatic carcinoma was around 30%.⁴

More recently intraoperative frozen section diagnosis has been restricted to those at high risk of metastases; lymphadenectomy with postoperative paraffin section diagnosis is undertaken as a staging procedure.

Our aim in this study was to assess the results of these two approaches, in particular considering the performance of frozen section by the same standards used for other diagnostic tests (sensitivity, specificity, and positive predictive value), as defined by Wilson and Jungner.⁵ An audit of the number of cases of undetected lymph node metastasis when staging lymphadenectomy was performed in the absence of frozen section diagnosis was undertaken, together with a cost analysis of detecting each case of metastatic carcinoma by frozen section.

Methods

All cases presented in this study underwent histopathological examination at UCL Hospitals NHS Trust, London. From 1987 to 1997 intraoperative frozen section diagnosis was performed on the pelvic lymph node dissection in 82 cases. Examination of routine paraffin sections without frozen section was performed in 195 cases.

FROZEN SECTION

The bilateral specimens for frozen section measured approximately 40×40×20 mm. Individual nodules were sometimes palpable but more often would appear macroscopically to be composed just of adipose tissue. Indeed the lymph nodes when present were often found to be partly replaced by fat, and dissection of individual lymph nodes was not possible. Any firm or white areas would be selected, along with palpable nodules, to produce up to 6-8 small blocks from each side. These would all be examined, resulting in up to 6-8 frozen sections per case. The average time from receipt of the lymph nodes to issue of a report was of the order of one hour. After frozen section all remaining tissue was fixed in formalin and processed for subsequent examination.

PARAFFIN SECTIONS

Examination just of paraffin processed lymph node tissue was introduced latterly in radical prostatectomy cases where preoperative biopsy showed a Gleason score of less than 7 and where there were no clinical factors suggesting metastatic disease. The entire lymphadenectomy specimen was received fixed in 10% formal saline, embedded, processed routinely to

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Table 1 Calculation of performance criteria for frozen section examination of pelvic lymph nodes at radical prostatectomy⁵

Frozen section diagnosis (test result)	Findings on paraffin sections (outcome)	
Positive: 6 cases	True positive (TP): 6 cases	False positive (FP): 0 cases
Negative: 76 cases	False negative (FN): 4 cases	True negative (TN): 72 cases
False negative rate:	$FN/(TP+FN) \times 100\%$	40%
Sensitivity:	$TP/(TP+FN) \times 100\%$	60%
Specificity:	$TN/(TN+FP) \times 100\%$	100%
Positive predictive value:	$TP/(TP+FP) \times 100\%$	100%

paraffin, and 5 µm sections cut and stained with haematoxylin and eosin.

FURTHER INVESTIGATION

If the diagnosis of metastasis was equivocal, either in the material obtained for frozen section or in the “routine” paraffin block sections, immunohistochemistry for prostate specific antigen and prostate specific acid phosphatase was performed.

Results

Intraoperative frozen section was requested in 82 patients and metastatic tumour identified in six on cryostat sections. On subsequent paraffin sections the frozen section results for carcinoma were all confirmed, representing the group of true positive cases. In the paraffin sections from all the other frozen section cases an additional four cases of metastatic carcinoma were identified, representing the false negatives. In one case, in retrospect, the carcinoma was present in the frozen section; in the others the diagnosis was made on examination of additional levels/blocks. There were no false positive diagnoses. These results were analysed according to the criteria used for assessing the performance of a diagnostic test (table 1).³ By these means the positive predictive value was found to be 100% and the specificity 100%, but the false negative rate was 40% and the sensitivity 60%.

ECONOMIC COST OF FROZEN SECTION

The marginal cost of theatre time at UCL Hospitals Trust is of the order of £500/hour, and the pathology cost for frozen section around £50. The additional time taken for the frozen section is around 82 hours for the entire series (one hour per case). This gives a cost of £7516 for detecting each case of metastatic carcinoma by frozen section (£550 × 82/6).

INCIDENCE OF CLINICALLY UNRECOGNISED METASTATIC DISEASE

In the series of 195 patients who underwent radical prostatectomy and lymphadenectomy without frozen section, metastatic tumour was found in nine cases (4.6%).

Discussion

The false negative rate of 40% is at the higher end of the range reported for false negatives rates (table 2). These figures have been calculated from published figures by Hermansen and Whitmore.¹² It is interesting that in

Table 2 Reported false negative rate for frozen section diagnosis of pelvic lymph nodes at radical prostatectomy²

Report	Missed metastasis rate (No/total) (%)	False negative rate (%)
McLaughlin et al (1976) ⁶	4/30 (13)	19
Fowler et al (1981) ⁷	3/35 (9)	37.5
Catalona and Stein (1982) ⁸	11/59 (19)	40.7
Sadlowski et al (1983) ⁹	3/42 (7)	23.1
Kramolowsky et al (1984) ¹⁰	16/100 (16)	27.1
Epstein et al (1986) ¹¹	11/40 (27.5)	27.5
Current series	4/82 (4.8)	40

many of the original series the authors gave a figure for the incidence of missed metastases that was rather less than the false negative rate. Thus in the current series the incidence of missed metastases would be only 4.8%.

The false negative rate on frozen section can be explained by difficulties with sampling, technical problems in taking cryostat sections of tissue with a large component of fat, and infiltration of the nodes by small neoplastic acini associated with sclerosis. It is unlikely that solutions to any of these problems will be found. Indeed, with improved patient selection it is likely that the false negative rate would be even worse, as affected lymph nodes would only show very small metastatic deposits.¹³

The economic cost of detecting each case of metastatic disease by frozen section is high, with a notional cost of £7516. Loss of operating time may be reduced by employing multiple teams of biomedical scientists, but this would increase the cost to the histopathology laboratory (though not to the same extent as the cost of theatre time). The use of cytology touch preparations as a speedier alternative to frozen section diagnosis is largely untried.

However, in the absence of frozen section 4.6% of patients will have had radical surgery in the presence of lymph node metastasis. It is highly likely that a proportion of these patients would not have been identified by frozen section, for reasons that have already been discussed. It is interesting to note that with current methods of selection of patients for radical prostatectomy the incidence of pelvic lymph node metastasis is significantly lower than was the case some 15 to 20 years earlier.^{3, 4} This observation strengthens the argument that there is a lesser need for intraoperative frozen section diagnosis of pelvic lymph nodes at the time of radical prostatectomy. Follow up of patients with microscopic lymph node metastases may show whether the survival advantage of radical prostatectomy in this context suggested by Cheng et al¹⁴ can be supported.

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