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

M P A Young, R S Kirby, E P N O'Donoghue, M C Parkinson

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.

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
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 Hermans and Whitmore.11 It is interesting that in 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.34 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.

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

<table>
<thead>
<tr>
<th>Frozen section diagnosis (test result)</th>
<th>Findings on paraffin sections (outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive: 6 cases</td>
<td>True positive (TP): False positive (FP): 6 cases: 0 cases</td>
</tr>
<tr>
<td>Negative: 76 cases</td>
<td>False negative (FN): True negative (TN): 4 cases: 72 cases</td>
</tr>
<tr>
<td>False negative rate:</td>
<td>FN/(TP+FN) × 100%</td>
</tr>
<tr>
<td>Sensitivity:</td>
<td>TP/(TP+FN) × 100%</td>
</tr>
<tr>
<td>Specificity:</td>
<td>TN/(TN+FP) × 100%</td>
</tr>
<tr>
<td>Positive predictive value:</td>
<td>(TP+FP)/100%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Report</th>
<th>Missed metastasis rate (No/total)</th>
<th>False negative rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLaughlin et al (1976)</td>
<td>4/30 (13)</td>
<td>19</td>
</tr>
<tr>
<td>Catalona and Stein (1982)</td>
<td>11/59 (19)</td>
<td>40.7</td>
</tr>
<tr>
<td>Sadlowski et al (1983)</td>
<td>3/42 (7)</td>
<td>23.1</td>
</tr>
<tr>
<td>Kromulowsky et al (1984)</td>
<td>16/100 (16)</td>
<td>27.1</td>
</tr>
<tr>
<td>Epstein et al (1986)</td>
<td>11/40 (27.5)</td>
<td>27.5</td>
</tr>
<tr>
<td>Current series</td>
<td>4/82 (4.8)</td>
<td>40</td>
</tr>
</tbody>
</table>

Lymph node frozen sections at prostatectomy


Royal College of Pathologists

Forthcoming symposia to be held at 2 Carlton House Terrace, London SW1:

Pulmonary pathology: 7 October 1999
Understanding stillbirth—is there progress?: 20 October 1999
Genomics in therapy and xenotransplantation: safety and ethics: 24 November 1999
Can't give a cause of death—won't give a cause of death: 12 January 2000
Molecular genetics of solid tumours: translating research into clinical practice: 24 February 2000
Managing immunodeficiency: 22 March 2000
Histopathology update: GI and hepatobiliary update and controversies: 13–14 April 2000

These meetings are open to members and non-members of the college. Further details and application forms from:
Scientific Meetings Officer, RCPath, 2 Carlton House Terrace, London SW1Y 5AF, UK; tel +44 (0)171 930 5862, ext 24/25; fax +44 (0)171 321 0523.