Who to treat with adjuvant therapy in Dukes B/stage II colorectal cancer? The need for high quality pathology

Eva J A Morris, Nicola J Maughan, David Forman, Philip Quirke

Objective: To identify by routine pathology which Dukes B colorectal cancer patients may benefit from chemotherapy.

Method: Retrospective study of the five year survival of colorectal cancer patients for whom colorectal pathology minimum datasets had been collected between 1997 and 2000 in the Yorkshire region of the UK.

The study population consisted of 1625 Dukes B and 480 Dukes C patients who possessed one positive node treated between 1997 and 2000. The predictive ability of the Petersen prognostic model was investigated and survival of Dukes B patients with potentially high risk pathological features was compared to that of Dukes C patients with one positive node.

Results: Only 23.3% of patients had all the pathological variables required for the application of Petersen’s index reported. The index offered a statistically significant survival difference of 24.3% and 30.3% between high and low risk colon (p<0.01) and rectal cancer patients (p<0.01). The size of these effects was smaller than predicted by the original model. Survival of Dukes B patients with any of the high risk pathological factors or low nodal yields was lower than that of Dukes C patients who possessed one positive node.

Conclusion: Petersen’s index discriminated between high and low risk Dukes B colorectal tumours, but inadequate pathological reporting diminished its ability to identify all high risk patients. The survival of patients with any high risk feature was lower than the threshold for adjuvant therapy of one lymph node positive Dukes C colorectal cancer. Chemotherapy may benefit patients with such features. Improving the quality of pathological reporting is vital if high risk patients are to be reliably identified.

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reatment for colorectal cancer is currently dictated by stage. Surgery is the only curative treatment but depending on the extent of disease there may be a role for adjuvant therapy. Dukes A (stage I) patients are treated with surgery alone while patients in the latter stages of C or D (stages III or IV) can have improved survival with postoperative chemotherapy. The role of adjuvant treatment in the management of Dukes B (T3 or T4 N0 (stage II)) patients is, however, controversial because of conflicting results from clinical trials and population based studies.

Dukes stage B encompasses a wide range of tumours. Some may just penetrate the muscular coat of the bowel wall while others may show extramural spread. Other factors may also have a large effect on prognosis and it is possible that the benefit of postoperative chemotherapy may vary in relation to this. In most populations around 35% of patients present with Dukes B stage disease, thus affecting 12 000 patients per year in the United Kingdom. To subject all these individuals to chemotherapy may be inappropriate when only a few may benefit.

In an attempt to resolve this problem Petersen et al undertook a prospective study of 268 Dukes B colon cancer patients and endeavoured to delineate the high risk individuals who would benefit from adjuvant treatment. Each tumour was carefully dissected and reported by a single gastrointestinal histopathologist. The pathological characteristics of the tumours were then related to survival and a prognostic model developed. Four factors were identified: tumour perforation, peritoneal involvement, venous spread and surgical margin involvement. Dukes B tumours with none of these characteristics had a comparable prognosis to Dukes A tumours while the presence of the high risk factors reduced the five year survival to 49.8%.

Before such an index can be used as a basis for selecting patients for adjuvant treatment, however, it is important for it to be validated in independent datasets. Since 1995 Yorkshire pathologists have been submitting proformas of the Yorkshire colorectal minimum dataset variables to the Northern and Yorkshire Cancer Registry and Information Service (NYCRIS). This provides an independent colon cancer dataset (derived from a wide population and representative of the range in the quality of reporting by pathologists) in which to validate the model. As rectal tumours are also reported it also allowed us to investigate if the Petersen index is transferrable to rectal cancer.

In addition, the dataset provided an opportunity to explore other potential ways of discriminating those Dukes B patients who may benefit from chemotherapy. The survival benefit of chemotherapy for Dukes C patients is proven. The possession of a single positive node defines the threshold for a Dukes C case and the greater the number of involved nodes the worse the prognosis of the patient. Patients with only one positive node are, therefore, automatically considered for chemotherapy and possess the best prognosis among patients with this stage of disease. If we can define Dukes B patients with any individual feature that predicts a prognosis worse or equivalent to that of a single positive node Dukes C it may simplify the selection of cases. Single features may be more valuable than formulas that can be compromised by missing data. Thus we have investigated Petersen’s formula in colon cancer for validation purposes and applied it to rectal cancer to determine if it is predictive in this population too. Finally, we have looked at a number of individual pathological features of Dukes B cancers to determine if these alone can predict outcome.

METHODS

The study population consisted of all Dukes B and C colorectal cancer (ICD10 codes C18, C19 and C20) patients with pathology
forms submitted and operated upon between 1997 and 2000 in the Yorkshire region of the UK. The Dukes C population was confined to those patients who had a single positive node identified. The population was analysed in three groups: colon (C18), rectosigmoid and rectal (C19 and C20) and all patients combined (C18, C19 and C20). Survival time was calculated from date of surgery to date of death or when censored (9 February 2006). Cancer specific survival was used to emulate Petersen’s methods with a cancer death being classified as one in which cancer was mentioned in any field on the death certificate. This was slightly different from that used by Petersen where cancer related deaths were defined according to clinical follow-up or autopsy reports.

Initially, the pathological characteristics of our populations were compared to that of Petersen and univariate survival analyses run to compare survival across groups. The data were then fitted into the Petersen index (table 1) and its predictive ability assessed. Within these models, if any variable for a patient was not reported it was assumed to be negative.

The survival of patients with potentially high risk pathological characteristics within our Dukes B population was compared to that of our Dukes C population who had a single positive lymph node. The high risk factors were those identified within Petersen’s study of peritoneal involvement, extramural vascular invasion, tumour perforation and involvement of resection margins. In addition, as the number of nodes retrieved from a specimen has been shown to affect the stage allocation of patients9 and relate to survival10–12 the impact of differing nodal yields was also investigated.

Dukes C patients are automatically considered for chemotherapy, whereas Dukes B patients are not. It was likely, therefore, that a large proportion of our Dukes C population may have had adjuvant chemotherapy and this may have confounded these survival comparisons. Finally, therefore, we took information from NYCRIS on the use of postoperative chemotherapy and stratified our population into those who received this treatment and those who did not. Survival in these groups across disease stages was then also examined.

## RESULTS

Between 1997 and 2000 Yorkshire’s pathologists returned colorectal pathology minimum datasets for 4469 colorectal tumours. Of these, 1086 were reported to be colon and 539 rectal or rectosigmoid Dukes B tumours and form the basis of our study population. Four hundred and eighty patients were identified within the pathology database as possessing one positive node; these patients form the basis of our Dukes C population. Eighty pathologists reported on the study population with the number of forms submitted by individual pathologists ranging from one to 108 (median 14.5).

Table 2 shows how the characteristics of our study population compared to that of Petersen. The populations were similar in relation to age and sex but the completeness of pathological reporting was much lower in the Yorkshire population. All variables in the Petersen series were reported. In contrast, in the Yorkshire data, peritoneal involvement was not reported in 10.2% of colon and 13.9% of rectal cases, vascular invasion in 9.0% of colon and 7.6% of rectal cases, margin status in 3.9% of colon and 3.3% of rectal cases and tumour perforation in 73.3% of colon and 71.4% of rectal cases. Only 378 (23.3%) out of the total Dukes B population had reports of all the pathological variables that Petersen identified as important.

There was also a statistically significant difference in the mean number of nodes retrieved from the two populations. The mean from the Petersen population was 21.3 in contrast to 11.5 in the colon and 11.8 in the rectal Yorkshire populations.

Likewise, there was a significant difference in the five year survival between the Petersen and Yorkshire populations. 76.1% of the patients (95% CI 70.0% to 81.0%) involved in the Petersen study survived for five years compared to only 67.4% (95% CI 65.0% to 69.9%) of Yorkshire’s colorectal cancer patients.

Table 3 shows the univariate five year survival for each of the prognostic factors across the different populations. In the Yorkshire population those patients who do not have a prognostic factor reported tend to have an intermediate survival between those possessing the factor and those who do not.

Table 4 shows how the survival estimated in the Petersen population compares to that in the Yorkshire population when fitted to the Petersen model. In the original population the index offered a 35.9% survival difference between the low and high risk groups it delineated. When this model was run across the Yorkshire data a statistically significant 24.3% difference in survival was observed between the high and low risk colon cancer populations (p<0.01). Likewise, a 30.3% difference in survival was observed by Petersen’s high and low risk groups in the rectal cancer population (p<0.01).

Figure 1 shows the five year survival curves of Dukes B patients with the high risk characteristics identified by Petersen compared to the five year of survival of those Dukes C patients who were found to have only one positive node and, hence, the best prognosis of all Dukes C patients. The five year survival of Dukes B patients who possessed any of the high risk pathological factors was worse than that of the single node positive Dukes C patients.

Table 5 shows the five year survival of Dukes B patients falling into different nodal yield categories. Across both cancer sites patients with few lymph nodes retrieved had significantly worse survival than patients with larger numbers of nodes recovered. For example, patients who had none to three nodes retrieved had a five year survival of 45.4% (95% CI 36.9% to 53.5%) compared to 79.3% (95% CI 74.8% to 83.1%) for patients with greater than 15 nodes examined (p<0.01). The survival of Dukes C patients with one positive node identified was 57.9% (95% CI 53.3% to 62.3%). Dukes B patients with fewer than four nodes retrieved, therefore, have poorer survival than the best prognosis Dukes C patients.

Dukes C patients are automatically considered for chemotherapy whereas Dukes B patients are not. Since the use of chemotherapy may have been confounding these survival comparisons, the influence of this treatment was also investigated. Across the entire Dukes B cohort 9.9% of the population received chemotherapy but this figure increased to 16.8% in the high risk Dukes B cohort; 41.3% of the single node positive Dukes C patients received chemotherapy. This was a smaller proportion than anticipated and so the mean age of the patients who received chemotherapy was compared to that of those who did not. There was a significant difference between the groups with the mean age of those receiving chemotherapy being 63.9 years (95% CI 62.6 to 65.2) compared to 74.8 years (95%
CI 73.7 to 75.9). This may indicate that Dukes C patients not receiving chemotherapy possessed greater comorbidity and were frailer than those who did receive this adjuvant treatment. Figure 2 illustrates the five year survival of these patients. Overall, the survival of high risk Dukes B patients was worse than the stage C patients in both the treated and untreated groups. The survival of high risk Dukes B and single node positive Dukes C patients was not significantly different in those who received chemotherapy (p = 0.23) but it was in those who did not receive chemotherapy (p = 0.05).

**DISCUSSION**

The original Petersen model predicted a statistically significant difference in survival between high and low risk Dukes B colon cancer patients. When the Yorkshire colon and rectal data were fitted to the model significant survival differences were observed but the magnitude of the effects was diminished. This confirms the value of the Petersen model in a considerably larger population based dataset of colon cancers and, for the first time, demonstrates its value in rectal cancer. Inadequate pathological reporting in our study population, however, diminished its ability to identify all high risk patients. The quality of pathological reporting must, therefore, be improved if all high risk patients are to be reliably identified.

Furthermore, the five year survival of Dukes B patients with any one of the high risk factors identified by Petersen or from whom fewer than four lymph nodes were retrieved was below the survival of Dukes C patients who possessed only one positive node. As patients with a single positive node are automatically considered for chemotherapy and receive a survival benefit from its application it would seem judicious to also give chemotherapy to all Dukes B patients with peritoneal involvement, extramural vascular invasion, tumour perforation or involved margins or in whom the lymph node yield is exceptionally low.

There are, however, a number of caveats to these conclusions; all centre on the quality of pathological reporting and the retrospective nature of our data. Firstly, the pathological variables deemed by Petersen et al as important in distinguishing between high and low risk Dukes B patients were poorly reported in our population, with only 23.3% of patients having the status of all the factors recorded. The scoring system within the Petersen index required us to assume that if a pathological factor was not recorded it was not present. For all the factors deemed prognostic by Petersen the Yorkshire patients in whom this information was not reported have an intermediate survival between those possessing the factor and those who do not. This suggests that absence of reporting does not necessarily mean the absence of the factor. In consequence, our high risk population was much smaller than that identified by Petersen et al with only 8.9% of colon and 8.4% of rectal cancer patients falling into this category compared to 28.7% of the Petersen population. This suggests that a large number of Yorkshire patients were not identified as high risk because of inadequate pathological reporting.

Differences in the quality of the reporting were also obvious elsewhere in the study. For example, extramural venous
Table 3
Univariate analysis of pathological prognostic factors

<table>
<thead>
<tr>
<th>Factor Category</th>
<th>Petersen (colon)</th>
<th>Yorkshire (colon)</th>
<th>Yorkshire (rectal)</th>
<th>Yorkshire (colorectal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival (95% CI)</td>
<td>89.3 (78.7 to 94.7)</td>
<td>71.0 (63.7 to 77.4)</td>
<td>67.4 (60.5 to 73.3)</td>
<td>61.1 (54.3 to 67.4)</td>
</tr>
<tr>
<td>5 mm</td>
<td>76.9 (70.1 to 83.1)</td>
<td>70.3 (63.7 to 77.4)</td>
<td>68.9 (60.5 to 75.3)</td>
<td>62.1 (54.3 to 69.7)</td>
</tr>
<tr>
<td>10 mm</td>
<td>61.5 (48.7 to 72.0)</td>
<td>57.5 (50.7 to 63.7)</td>
<td>54.1 (45.4 to 62.8)</td>
<td>51.1 (43.4 to 58.8)</td>
</tr>
<tr>
<td>15 mm</td>
<td>46.8 (34.8 to 58.8)</td>
<td>43.5 (35.8 to 51.1)</td>
<td>41.5 (33.6 to 49.4)</td>
<td>39.3 (31.6 to 47.1)</td>
</tr>
<tr>
<td>20 mm</td>
<td>34.4 (22.4 to 46.4)</td>
<td>31.4 (23.5 to 39.3)</td>
<td>29.2 (20.6 to 37.9)</td>
<td>27.1 (19.3 to 34.9)</td>
</tr>
<tr>
<td>Not reported</td>
<td>69.0 (62.6 to 73.3)</td>
<td>64.5 (57.8 to 70.0)</td>
<td>61.5 (53.8 to 68.4)</td>
<td>58.4 (50.6 to 66.2)</td>
</tr>
<tr>
<td>Peritoneal involvement</td>
<td>Present</td>
<td>89.3 (78.7 to 94.7)</td>
<td>71.0 (63.7 to 77.4)</td>
<td>67.4 (60.5 to 73.3)</td>
</tr>
<tr>
<td>Not reported</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rectal perforation</td>
<td>Present</td>
<td>61.5 (48.7 to 72.0)</td>
<td>57.5 (50.7 to 63.7)</td>
<td>54.1 (45.4 to 62.8)</td>
</tr>
<tr>
<td>Not reported</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tumour invasion</td>
<td>Extent of spread beyond muscularis propria</td>
<td>5 mm</td>
<td>61.5 (48.7 to 72.0)</td>
<td>57.5 (50.7 to 63.7)</td>
</tr>
<tr>
<td>Not reported</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Margin involvement</td>
<td>Present</td>
<td>46.8 (34.8 to 58.8)</td>
<td>43.5 (35.8 to 51.1)</td>
<td>41.5 (33.6 to 49.4)</td>
</tr>
<tr>
<td>Not reported</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tumour perforation</td>
<td>Present</td>
<td>34.4 (22.4 to 46.4)</td>
<td>31.4 (23.5 to 39.3)</td>
<td>29.2 (20.6 to 37.9)</td>
</tr>
<tr>
<td>Not reported</td>
<td>-</td>
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</table>

Note: The data are presented as survival percentage (95% confidence interval).

Improving the quality of pathological examination and reporting substantially diminish its ability to identify all high risk patients, reducing the number of high risk cases from 28.7% to 8.7%.
is vital if both routine pathology and the index are to be used to inform clinical practice. A pathology education programme with audit may achieve this.28

A final problem is the retrospective nature of our data. This particularly impacts on our ability to draw definitive conclusions on the survival differences observed between high risk Dukes B and single node positive Dukes C patients. As a result of selection bias the comparison of treated and untreated populations in a setting outside a randomised controlled trial is potentially flawed. Ideally, therefore, all patients who had adjuvant treatment should have been excluded from the analyses otherwise one could argue it was the chemotherapy and not the pathology that was responsible for the survival differences. In our study, however, it was the younger patients who tended to be given chemotherapy and excluding this group would equally have confounded the study. Furthermore, consistently poorer survival differences were observed between Dukes C and high risk Dukes B patients in both those receiving and those not receiving chemotherapy. As such, our results are important to inform the debate surrounding the clinical dilemma of which Dukes B patients to treat. Evidence suggests significant proportions of Dukes B patients already receive treatment that may be inappropriate when only a subgroup of the Dukes B population may benefit.3

So; in the absence of excellent pathology or high quality randomised trials in this area a pragmatic interim solution may

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of survival between the low and high risk populations derived from the Petersen index across the two study populations (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Petersen Yorkshire (colon)</td>
</tr>
<tr>
<td>Low</td>
<td>85.7 (79.4 to 90.2)</td>
</tr>
<tr>
<td>High</td>
<td>49.8 (37.0 to 61.3)</td>
</tr>
<tr>
<td>Total</td>
<td>76.1 (70.0 to 81.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Five year survival of patients with different nodal yields (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>Number of nodes retrieved</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Dukes B</td>
<td>0–3</td>
</tr>
<tr>
<td></td>
<td>4–6</td>
</tr>
<tr>
<td></td>
<td>7–9</td>
</tr>
<tr>
<td></td>
<td>10–12</td>
</tr>
<tr>
<td></td>
<td>13–15</td>
</tr>
<tr>
<td></td>
<td>&gt;15</td>
</tr>
<tr>
<td>Dukes C</td>
<td>1 positive node</td>
</tr>
</tbody>
</table>

Figure 1 Survival of Dukes B colorectal cancer patients compared to Dukes C colorectal cancer patients who possess only one positive node.
be to recommend treatment on the basis of any individual high risk features. If the minimum treatment criterion is a single positive lymph node then any pathological feature that conferred a worse prognosis than possession of a single positive node should be an indication for adjuvant therapy. We found the prognosis of patients with the features identified by Petersen (table 3) to be worse than that of Dukes C patients with a single positive node and there was no statistically significant difference when the potentially confounding influence of chemotherapy was also considered. Treating all Dukes B patients with these factors may, therefore, improve survival and would lead, based on the Yorkshire data, to approximately an additional 8% of all colorectal cancer patients being considered for adjuvant treatment. Retrieving more lymph nodes would also increase the number of people offered chemotherapy as it would increase the percentage of Dukes C cases.

Complex prognostic indices are currently being developed which examine molecular aspects of tumours that will delineate which patients are high risk and will benefit from chemotherapy. Determining eligible patients via these indices will require expensive tests and, consequently, be costly to healthcare providers. In contrast, routine pathology is already available to all colorectal cancer patients. The Yorkshire data suggest improvements in this service alone are likely to improve outcomes. Good pathology should ensure more accurate stage allocation and ensure that all Dukes C patients are correctly identified and offered the potentially beneficial chemotherapy indicated. Likewise, the adequate pathological reporting of Dukes B patients would enable the stratification of patients into high and low risk groups using models such as Petersen’s. If pathology cannot be improved to such standards then the use of individual pathology features for the selection of high risk Dukes B cases will go some way to ameliorating the impact on patients.

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Figure 2 Kaplan-Meier survival curves for high risk Dukes B and single node positive Dukes C patients who did and did not receive adjuvant chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>Number at risk</th>
<th>Survival probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukes C with chemotherapy</td>
<td>26 25 19 18 18 18</td>
<td>0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0</td>
</tr>
<tr>
<td>Dukes C with chemotherapy</td>
<td>198 195 176 164 152 143</td>
<td></td>
</tr>
<tr>
<td>High risk Dukes B without chemotherapy</td>
<td>116 74 55 44 41 38</td>
<td></td>
</tr>
<tr>
<td>Dukes C without chemotherapy</td>
<td>282 201 173 147 127 113</td>
<td></td>
</tr>
</tbody>
</table>

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Competing interests: none.

REFERENCES

Which Dukes B to treat


**EDITOR’S QUIZ: GI SNAPSHOT**

**Answer**

From question on page 1409

At this point, the diagnosis of intraductal polypoid lesion was suspected, and the patient underwent common bile duct exploration that revealed a polypoid tumour protruding from the left hepatic duct (LHD). A left liver resection combined with en bloc resection of the extrahepatic biliary tree was performed. The resected specimen contained a solitary polypoid tumour from the bile duct, leading to biliary obstruction, and necessitates combined liver and bile duct resection for complete excision. Its prognosis is not known.

Intraductal polypoid tumours are mainly represented by papillary-type cholangiocarcinoma and hepatocellular carcinoma with bile duct invasion. MHC is known as a rare primary liver tumour that is usually associated with chronic liver disease. The lesion behaves as a parenchymal mass and has characteristic biological markers and radiological features according to the predominant component. Curative treatment involves liver resection. In contrast, intraductal MHC originates from the bile duct, leads to biliary obstruction, and necessitates a combined liver and bile duct resection for complete excision. Its prognosis is not known.

**Figure 1** Macroscopic appearance of the polypoid tumour originating from the left hepatic duct, spreading into the lumen and protruding into the main hepatic duct.

**Figure 2** Microscopic view of the tubular pattern of the cholangiocarcinoma component (H&E, X400).

**Figure 3** Microscopic view of the trabecular pattern of the hepatocellular carcinoma component (H&E, X400).

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