Invited Review

Detection and significance of minimal residual disease in colorectal cancer

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Summary. Colorectal cancer (CRC) is one of the most common causes of cancer death in the developed world. Although the primary treatment for CRC is surgical, disease relapse due to minimal residual disease (MRD) following apparently curative surgery occurs in up to fifty percent of patients. Most patients who develop overt metastases beyond the regional lymph nodes eventually die of the disease. At present adjuvant chemotherapy is used to improve survival in patients with metastases to regional lymph nodes demonstrated by routine histopathology with no other evidence of spread. The ability to identify metastatic disease at an earlier stage could be of considerable benefit in directing adjuvant therapy to patients at high risk of relapse who are not identified by current methods. Several techniques have been developed for the detection of MRD, including immunohistochemical and molecular methods, however their role in clinical practice is not yet established. The purpose of this paper is to review these techniques and their potential clinical use in the management of CRC.

Key words: Colorectal cancer, Metastases, Minimal residual disease, Prognostic markers

Introduction

Staging of colorectal cancer

Disease stage is the most important predictor of outcome after surgery for colorectal cancer (CRC). The Dukes staging system for rectal cancer (Dukes, 1932) identified the essential elements of penetration through the bowel wall and the presence of lymph node metastases. Since that time many modifications and subclassifications have been proposed, all with the aim of improving prognostic accuracy (Table 1). However these staging systems have resulted in only limited improvements in prognostic accuracy when compared with the original Dukes system (Onodera et al., 1989).

The importance of accurate staging

Prognostic information is most useful when it enables identification of patients who can be treated more aggressively with the expectation of improving outcome (Jass, 1995). In CRC the advent of effective adjuvant therapy in histologically proven lymph node positive disease has heightened the importance of this prognostic indicator (NIH consensus conference, 1990). However, the problem remains that up to 40% of patients with histologically node negative CRC eventually die of recurrent disease (Newland et al., 1987). This is thought to be due to the presence of minimal residual disease (MRD) at the time of surgery, which is not detected by conventional histological or imaging techniques (Finlay and McCandie, 1986). The need for more sensitive and specific prognostic information is therefore real because adjuvant therapy could be targeted more effectively to those patients with the highest likelihood of benefit.

New prognostic markers

In recent years much work has been done on CRC trying to develop new prognostic markers utilising research which has broadened the understanding of basic tumour biology (Fielding, 1998). Efforts were made in 1995 by the College of American Pathologists to review the available work and assess its potential clinical applicability (Fielding and Pettigrew, 1995). However, even since that time over 1000 citations can be found on a Medline search with reference to CRC and the newer biological variables. These include markers of differentiation (van Belzen et al., 1998), proliferation (Shepherd et al., 1988; Mayer et al., 1993), angiogenesis (Frank et al., 1995; Kumar et al., 1998), metastatic potential (Dorudi et al., 1993; Tanabe et al., 1993) and the presence or absence of tumour suppressor genes (Yamaguchi et al., 1992; Poller et al., 1997). Although some of the newer markers have proved to have
Table 1. Staging systems in colorectal cancer.

<table>
<thead>
<tr>
<th>STAGING SYSTEM</th>
<th>TYPE</th>
<th>FEATURES</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukes P</td>
<td></td>
<td>Depth of penetration of primary tumour</td>
<td>Dukes, 1932</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence of lymph node metastases</td>
<td></td>
</tr>
<tr>
<td>Gabriel and Dukes P</td>
<td></td>
<td>Division of Dukes' C into C1 and C2 by apical node involvement</td>
<td>Gabriel et al., 1935</td>
</tr>
<tr>
<td>Astler and Coler P</td>
<td></td>
<td>Division of Dukes' C into C1 and C2 by depth of penetration of primary tumour</td>
<td>Astler and Coler, 1954</td>
</tr>
<tr>
<td>Turnbull modification CP</td>
<td></td>
<td>Addition of stage D to identify distant metastatic disease</td>
<td>Turnbull et al., 1967</td>
</tr>
<tr>
<td>Australian Clinico-CP</td>
<td></td>
<td>Depth of penetration of primary tumour</td>
<td>Davis and Newland, 1983</td>
</tr>
<tr>
<td>Pathological Staging System</td>
<td></td>
<td>Presence and location of lymph node metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence of distant metastases or incomplete excision</td>
<td></td>
</tr>
<tr>
<td>Jass P</td>
<td></td>
<td>Depth of penetration of primary tumour</td>
<td>Jass et al., 1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence and number of lymph node metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Characteristic of tumour margin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence of peritumoral lymphocytic infiltrate</td>
<td></td>
</tr>
<tr>
<td>TNM CP</td>
<td></td>
<td>Depth of penetration of primary tumour</td>
<td>UICC, 1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasion of adjacent structures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence, number and location of lymph node metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence of distant metastases</td>
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<td>Invasion of adjacent structures</td>
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<td></td>
<td></td>
<td>Presence and location of lymph node metastases</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Presence of distant metastases</td>
<td></td>
</tr>
</tbody>
</table>

CP: clinicopathological; P: pathological.

prognostic potential, traditional pathological variables remain the gold standard with the presence or absence of histologically evident lymph node metastases the most important determinant of survival in patients without evidence of distant metastases (Fielding et al., 1986).

Detection of minimal residual disease

Given the importance of lymph node metastases to prognosis and treatment of CRC, it is surprising that this aspect of tumour evaluation has not received more attention. Both the presence and number of histologically evident lymph node metastases have been shown repeatedly to be independent prognostic indicators of survival (Phillips et al., 1984; Fielding et al., 1986; Wolmark et al., 1986; Hyder et al., 1990; Cohen et al., 1991). Therefore to maximise detection of lymph node metastases and MRD, both the number of nodes examined and the technique of examination are of great importance.

Number of nodes examined

Work by Scott and Grace (1989) and Hermanek (1991) suggested that the minimum number of nodes that needed to be examined to obtain the most accurate histological nodal stage was 12 to 13. In a study of T3 CRCs Tang et al. (1995) showed that when 10 or more lymph nodes were sampled a mean of 5.4 nodes had metastases compared with a mean of 2.1 nodes if less than 10 nodes were sampled. Goldstein et al. (1996) also examined T3 CRC's and found that when between 1-4 lymph nodes were recovered 29% of patients had metastatic involvement, compared with 87% when 17-20 nodes were recovered. Using the same groupings Hermanek's findings were confirmed, but by narrowing the groupings they found that dissection of 17 lymph nodes gave the highest yield of positive nodes, suggesting that all possible nodes should be examined for histology.

Limitation in conventional histological analysis

Conventional histological analysis of lymph nodes is limited and involves sampling only an estimated 1/1000 of the tissue (Sloane, 1995). Determination of nodal status in these circumstances relies on morphological change to be apparent in a very small sample. If the disease is minimal, Gusterson and Ott (1990) calculated by mathematical modelling that a pathologist has a 1% chance of identifying a three cell diameter lymph node metastasis by routine methods. Clearly with such low probabilities for detecting small volume disease more sensitive diagnostic techniques are required.

These techniques include increased sampling by standard histology (serial sectioning, xylene clearance),
augmenting histological evaluation by immunohistochemistry and application of molecular techniques. The remainder of this review will summarise the use of these techniques in CRC.

**Histological detection of MRD**

**Clearance techniques**

Clearance of mesenteric fat by xylene (Cawthorn et al., 1986) aids lymph node identification, enabling an increased number of lymph nodes to be harvested. This has principally been employed as a research tool, though it is used routinely in some centres (Hyder et al., 1990). Initial studies on clearance techniques suggested that finding more nodes did not change the stage of disease, or necessarily increase the yield of lymph nodes (Cawthorn et al., 1986; Jass et al., 1986). However, more recent studies have shown both an increase in detection of positive nodes and change in disease stage compared with routine manual dissection (Haboubi et al., 1992; Hida et al., 1994). Such comparisons are only valid within each institution, and highlight differences in histopathological analysis. The study by Haboubi et al. (1992) had a low number of nodes detected by routine techniques (mean of 6.7 nodes per specimen), which may have exaggerated the relative benefits of using clearance techniques.

**Serial sectioning**

In breast cancer one large prospective trial has shown that serial sectioning of lymph nodes (six sections per node) increased the number of metastases detected compared to routine histology, and that nodal disease detected in this way had independent prognostic significance (Ludwig, 1990). Serial sectioning has not been widely studied in CRC, however Nicholson et al. (1994) and Broll et al. (1997) have both used this technique, taking three sections per node, in combination with immunohistochemistry. Nicholson et al. did not detect any additional metastases with a combination of the two techniques. Broll et al. detected evidence of MRD in 19% of the histologically node negative patients. However, it is not possible to ascertain how much of this was due to serial sectioning and how much was detected from the use of immunohistochemistry. In both of these studies undersectioning may partially account for the low rate of detection of MRD.

**Immunohistochemistry**

The principal method of investigation for MRD in CRC has been by immunohistochemistry with either tumour or cell type specific markers. In CRC there are currently no tumour specific markers that are expressed by all tumours; K-ras mutations are evident in 30-50% tumours, and p53 mutations in 50-70% tumours with a combined incidence of 50-70% (Hayashi et al., 1995). Cell type specific markers rely on differences of expression between different cell types, such as epithelial and lympho-haemopoietic cells. Various markers have been used including the tumour specific marker p53 (Clarke et al., 1997) and possibly CEA (Davidson et al., 1990; Cutait et al., 1991), and the cell type specific cytokeratins (Makin et al., 1989; Schlimok et al., 1990; Cutait et al., 1991; Lindemann et al., 1992; Haboubi et al., 1992; Greenson et al., 1994; Jeffers et al., 1994; Nicholson et al., 1994; O'Sullivan et al., 1995; Adell et al., 1996; Broll et al., 1997; Clarke et al., 1997). Cytokeratins are intermediate filament proteins expressed by epithelial cells and rarely expressed in lympho-haemopoietic cells (Traweek et al., 1993). They are primary components of the mammalian cell cytoskeleton and constitute a multigene family of proteins distinguished by their cell type-specific expression (Nagle, 1988). Cytokeratins show strict lineage and differentiation associated patterns of expression with malignant cells retaining the intermediate filaments of their progenitor type (Moll et al., 1982). For these reasons the expression of cytokeratins has been commonly used to characterise neoplastic cells of epithelial origin in non epithelial tissues (Cooper et al., 1985).

Cytokeratin immunohistochemistry has been used to detect occult lymph node and bone marrow metastases in breast cancer (Trojani et al., 1987; Cote et al., 1995b; Fox et al., 1997), gastric cancer (Jauch et al., 1996) and lung cancer (Cote et al., 1995; Pantel et al., 1996) and has in turn been associated with poorer prognosis (Cote et al., 1995a; Jauch et al., 1996; Pantel et al., 1996).

In CRC several studies have been performed with cytokeratin immunohistochemistry with variable results (Table 2). Four studies have shown a significant association between MRD detected using cytokeratin immunostaining and increased mortality (Schlimok et al., 1990; Lindemann et al., 1992; Greenson et al., 1994; Clarke et al., 1997). The mean incidence of MRD detected by immunohistochemical methods in these studies was 29.3%. In addition Lindemann et al. (1992) showed that immunohistochemically detection of MRD in bone marrow aspirates was of independent prognostic significance as a determinant of relapse.

Despite a similar mean rate of detection of MRD (27.5%) four other studies have found no association between survival and MRD detected by immunohistochemistry (Cutait et al., 1991; Jeffers et al., 1994; Adell et al., 1996; Broll et al., 1997). However, none of these studies had sufficient power to detect a clinically significant difference in survival between histologically node negative patients with, and without, MRD detected by immunohistochemistry. It is not clear in these studies if the primary tumour from each specimen was used as the positive control when assaying the lymph nodes. If the primary tumour was not used as a positive control it is not possible to differentiate between absence of metastases and absence of staining per se, resulting in under detection of MRD.

In comparison with the other studies Broll et al.
studies to date have not consistently shown benefit in found to be a significant indicator of recurrence (O'Sullivan et al., 1995). MRD in bone marrow was labour intensive and expensive and may not be practical to adopt in a diagnostic laboratory (Ludwig, 1990). However, due to processing techniques they could not retrospectively ascertain the number of lymph nodes examined per patient, which if low may account for the low level of detection of MRD. In the study by Adell et al. (1996) a mean of only 4.7 lymph nodes per patient were examined, with 93% of the study population having less than 10 nodes dissected per specimen. This limits the number of metastases that could potentially be detected (Tang et al., 1995; Goldstein et al., 1996).

The remaining two small studies (Makin et al., 1989; Nicholson et al., 1991) both used the antibody CAM 5.2 which detects cytokeratins 8, 18 and 19 (Makin et al., 1989). Neither study was able to demonstrate additional lymph node metastases.

Objective analysis of MRD detected by immunohistochemistry has been attempted by flow cytometry in both CRC (O'Sullivan et al., 1995, 1997) and breast cancer (Gross et al., 1995). MRD in bone marrow was detected in 28% of CRC (O'Sullivan et al., 1995), a level similar to that of immunohistochemical detection in lymph nodes. Post operative detection of MRD was found to be a significant indicator of recurrence (O'Sullivan et al., 1997).

In summary, histological methods of detecting MRD including clearance techniques, serial sectioning of lymph nodes and immunohistochemistry all appear to improve detection of lymph node metastases. However, studies to date have not consistently shown benefit in terms of prognostic accuracy, and many have been inadequate. Furthermore all of these techniques are labour intensive and expensive and may not be practical to adopt in a diagnostic laboratory (Ludwig, 1990).

Molecular detection of MRD

The polymerase chain reaction (PCR) offers potential advantages in the detection of MRD over immunohistochemistry. It is up to 100 fold more sensitive in the detection of malignant cells (Ghossein and Rosai, 1995), and when combined with reverse transcription (RT-PCR) can be used to assess for the presence of tissue or tumour specific transcripts from viable cells (Johnson et al., 1995). RT-PCR can detect down to 1 malignant cell/10^7 normal cells making it the most sensitive technique for the detection of MRD that has been developed. PCR, like immunohistochemistry, relies on accurate markers of malignant disease. The extremely sensitive nature of the technique means that very low level gene expression can be detected making specificity an important issue (de Graaf et al., 1997). In the design of any PCR protocol it is necessary to adhere to certain procedures in order to avoid false positives, namely; physical separation of various steps of the procedure, use of DNA free equipment and consumables, negative controls to assay for contamination, and in the case of RT-PCR, endogenous controls to monitor RNA extraction and cDNA synthesis.

In CRC a number of potential markers have been assayed using PCR. These can be divided into tumour specific markers such as K-ras and p53 (Hayashi et al., 1995), alternatively spliced CD44 (Wong et al., 1997), and possibly CEA (Gerhard et al., 1994; Mori et al., 1995; Jonas et al., 1996; Liefers et al., 1998), or tissue specific markers such as the cytokeratins (Burchill et al., 1995; Gunn et al., 1996; Soeth et al., 1996; Denis et al., 1997; Bustin et al., 1998; Dorudi et al., 1998). Although it is always preferable to use tumour specific markers, these are not universally expressed by colorectal tumours.

Tumour specific markers

Hayashi et al. (1995) used sophisticated PCR techniques on archival tissue to assess MRD in lymph nodes from 120 CRC patients using the tumour specific markers K-ras and p53. Only 60% of the tumours in the study group were informative for either of the markers, but in those that were informative, the presence of micrometastases in the regional lymph nodes was a

Table 2. Immunohistochemical studies in CRC.

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>YEAR</th>
<th>No. OF PATIENTS</th>
<th>TISSUE EXAMINED</th>
<th>% WITH MRD</th>
<th>WORSE PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makin et al.</td>
<td>1989</td>
<td>10</td>
<td>Lymph node</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Schlimok et al.</td>
<td>1990</td>
<td>156</td>
<td>Lymph node</td>
<td>27</td>
<td>Yes</td>
</tr>
<tr>
<td>Cutul et al.</td>
<td>1991</td>
<td>46</td>
<td>Lymph node</td>
<td>26*</td>
<td>No</td>
</tr>
<tr>
<td>Lindemann et al.</td>
<td>1992</td>
<td>88</td>
<td>Bone marrow</td>
<td>32</td>
<td>Yes</td>
</tr>
<tr>
<td>Green et al.</td>
<td>1994</td>
<td>50</td>
<td>Lymph node</td>
<td>28*</td>
<td>No</td>
</tr>
<tr>
<td>Jeffers et al.</td>
<td>1994</td>
<td>77</td>
<td>Lymph node</td>
<td>25*</td>
<td>Yes</td>
</tr>
<tr>
<td>Nicholson et al.</td>
<td>1994</td>
<td>33</td>
<td>Lymph node</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>Adell et al.</td>
<td>1996</td>
<td>100</td>
<td>Lymph node</td>
<td>39*</td>
<td>No</td>
</tr>
<tr>
<td>Broil et al.</td>
<td>1997</td>
<td>49</td>
<td>Lymph node</td>
<td>26.5 (19*)</td>
<td>Trend</td>
</tr>
<tr>
<td>Clarke et al.</td>
<td>1997</td>
<td>100</td>
<td>Lymph node</td>
<td>30*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*; percentage of patients in whom evidence of minimal residual disease (MRD) has been detected; †: Dukes' B patients only; ‡: used combination of p53 and cytokeratin staining.
Molecular markers in colorectal cancer

significant predictor of recurrence. The use of archival tissue in this study may well have lowered the frequency of mutations detected as PCR was not successful on all 120 patients.

CD44 is a cell adhesion glycoprotein that can occur in alternative spliced iso-forms (Matsumura and Tarin, 1992). The alternative splicing of this molecule has been the target for RT-PCR detection of MRD in blood and lymph nodes (Wong et al., 1997). However not all tumours exhibit the same splice variants (Wielenga et al., 1993; Tahara, 1995) and alternative splice variants have also been detected in normal controls (Rodriguez et al., 1995). Wong et al. (1997) did not find evidence of alternative spliced transcripts in the control groups, but these consisted only of blood from 8 volunteers and lymph nodes from 3 non CRC patients. These control samples are too few to exclude the possibility of alternative spliced CD44 expression in normal tissues and more work is required.

CEA gene expression has also been assessed as a marker for the detection of MRD (Gerhard et al., 1994; Mori et al., 1995; Neumaier et al., 1995; Jonas et al., 1996; Liefers et al., 1998). It does however show considerable variation in expression (Mafune et al., 1992) and has to be regarded with caution as a tumour specific marker. Mori et al. (1995) assayed for CEA expression in lymph nodes from 13 patients with either oesophageal, gastric, rectal or breast carcinomas. The median number of nodes examined per patient was only 6.5 and the control group consisted of 20 lymph nodes from patients without cancer. Although no expression was detected in the control group, the sample size is again too small to exclude illegitimate transcription with any certainty. Jonas et al. (1996) attempted to detect circulating tumour cells by CEA RT-PCR in peripheral blood. However, they showed that 23% of controls without cancer had evidence of CEA expression, which the authors propose may be due to venepuncture induced skin contamination. More recently Liefers et al. (1998) have reported the use of a nested CEA RT-PCR assay for the detection of MRD in lymph nodes. An average of 7.3 nodes per patient were examined potentially under-
staging the cases which had worse outcome (Goldstein et al., 1996). Only 7 lymph nodes from 2 patients were used as controls, and CEA expression was detected in these at high cycle numbers. Despite the absence of detection of CEA expression with the selected conditions, the control sample size is such that the true specificity of the assay has wide variability with 95% confidence limits of 15.8% to 100%. Despite this MRD detected by this method was a prognostic indicator of survival in stage II cancer. Due to the potential errors in this study these results must be treated with caution and confirmation by other studies is necessary.

Cell type specific markers

In the absence of a tumour specific DNA marker for all CRC, the PCR amplification of epithelial cell-specific RNA transcripts after reverse transcription (RT-PCR) has been reported as a sensitive and specific method of detecting occult metastases to non-epithelial tissues (Burchill et al., 1995; Gunn et al., 1996).

Most early work using RT-PCR in carcinomas has been with breast cancer targeting K19 (Datta et al., 1994; Schoenfeld et al., 1994; Noguchi et al., 1996). However recent studies have called into question the tissue specificity of K19 gene expression when analysed by these very sensitive tests. K19 transcripts have been frequently detected in control tissues on single round RT-PCR by ourselves (Fig. 1) and others (Burchill et al., 1995; Krißmann et al., 1995; Gunn et al., 1996; Yun et al., 1997).

Cytokeratin 20 (K20) has been reported as a gastrointestinal specific cytokeratin with expression detected by immunohistochemistry in 95% of CRC (Moll et al., 1982). When analysed by RT-PCR 100% of CRC have evidence of K20 gene expression (Burchill et al., 1995; Gunn et al., 1996; Dorudi et al., 1998). In addition, a large number of control subjects without cancer have been found not to exhibit K20 gene expression in lymph nodes (Dorudi et al., 1998; Merrie et al., 1998a), making this a highly suitable marker for occult lymph node metastases (Fig. 2). Dorudi et al. (1998) showed that 27% of histologically negative lymph nodes had evidence of K20 transcripts as detected by single round RT-PCR.

This is in keeping with our own results; to date we have studied 106 patients with CRC, 66 of whom had histologically node negative disease. One third of the histologically node negative patients have evidence of MRD as detected by K20 RT-PCR (Fig. 3). All patients with node positive disease have been detected by this technique. To test for specificity we have performed K20 RT-PCR on 248 lymph nodes from 39 patients without CRC. Only one node from 1 patient was positive for K20, and this was from a patient with a highly dysplastic villous adenoma. Even if this represents a false positive result, the specificity of the test in our hands exceeds 97.5% (Merrie et al., 1998b).

Recent reports suggest that K20 transcripts may be detectable by highly sensitive RT-PCR techniques at very low numbers in normal blood ( Denis et al., 1997; Bustin et al., 1998) and lymph nodes (Bustin et al., 1998). Denis et al. (1997) used a nested RT-PCR assay to reach the desired sensitivity, whereas Bustin et al. (1998) developed a unique highly sensitive fully quantitative fluorogenic 5'-nuclease RT-PCR assay. This has shown evidence of extremely low transcript numbers in peripheral blood from a small cohort of normal volunteers, distinguishable from patients with CRC. A further immunofluorescence study found normal K20 labelled cells in bone marrow at higher frequencies, but may suffer the crossreactivity problems inherent in any immunological assay (Little et al., 1997).

In order to utilise tissue specific markers using very sensitive molecular techniques a balance between sensitivity and specificity inevitably needs to be struck. K19 expression appears to lack the specificity required as a marker of MRD (Burchill et al., 1995; Gunn et al., 1996; Yun et al., 1997; Dingemans et al., 1997; Bustin et al., 1998) whereas K20 remains a potential marker in well controlled circumstances or with quantitative assays. Several groups are currently engaged in prospective clinical studies to determine whether K20 detected MRD will be a useful predictor of recurrent disease especially in histologically node negative patients.

Conclusion

The shortcomings of clinicopathological staging in CRC are readily apparent, however, none of the new biological markers have so far been sensitive or specific enough to be clinically useful. More sensitive detection of MRD may be able to meet this need, particularly in histologically node negative patients for whom adjuvant therapy is not routinely prescribed. The feasibility of using molecular techniques to detect submicroscopic metastases has been demonstrated in recent studies with the suggestion that MRD detected in this manner has prognostic value. Well designed clinical studies are needed to confirm these findings and determine what role molecular techniques could have in future clinical practise.

References


Burchill S.A., Bradbury M.F., Pittman K., Southgate J., Smith B. and...
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