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ANATOMICAL PATHOLOGY

Competing risks analysis of the effect of local residual tumour on recurrence and cancer-specific death after resection of colorectal cancer: implications for staging

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Summary

The pTNM staging system for colorectal cancer (CRC) is not entirely effective in discriminating between potentially curative and non-curative resections because it does not account for local residual tumour in patients with stages I, II or III. This study aimed to evaluate the prognostic importance of histologically verified tumour in any line of resection of the bowel resection specimen (TLR) in relation to pTNM stages and to demonstrate how TLR may be integrated into pTNM staging. Information on patients in the period 1995 to 2010 with complete follow-up to the end of 2015 was extracted from a prospective database of CRC resections. The outcome variables were the competing risks incidence of CRC recurrence and CRC-specific death. After exclusions, 2220 patients remained. In 1930 patients with pTNM stages I–III tumour, recurrence was markedly higher in those with TLR than in those without (HR 6.0, 95% CI 4.2–8.5, $p < 0.001$) and this persisted after adjustment for covariates associated with recurrence. CRC-specific death was markedly higher in the presence of TLR (HR 7.7, CI 5.3–11.2, $p < 0.001$), which persisted after adjustment for relevant covariates. These results justify removing patients with TLR from pTNM stages I to III and placing them in stage IV, thereby allowing the categorisation of all patients with any known residual tumour into three prognostically distinct groups. This study demonstrates how TLR may be integrated into pTNM staging, thus improving the definition of the three stages which are considered potentially curable (I, II and III).

Key words: Colorectal cancer; staging; local residual tumour; recurrence; prognosis.

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INTRODUCTION

The objective of tumour staging is to classify tumours anatomically into clearly defined groups which correlate with prognosis. Simplicity, enabling ease of recall, is seen as a desirable attribute of any staging system. The Dukes' staging system for resected colorectal cancer (CRC) specimens met these criteria but failed to address the important issue of defining and classifying the presence of known residual tumour (local or metastatic) at the time of bowel resection.[1] The first attempt to correct this deficiency was made by Turnbull in 1967, who modified Dukes' staging by creating a stage D for tumours with a very poor prognosis.[2] Stage D included tumours locally irresectable because of parietal invasion, those with adjacent organ invasion whether or not the cancer and adjacent organ were resected and those with distant metastasis detected clinically by the surgeon at the time of bowel resection. Therefore, it was a clinicopathological system. In 1971 we initiated a hospital-based study in which stage D tumours were defined as having either distant metastasis (substage D2) or local tumour remaining (substage D1).[3] The latter was determined by the selection of tissue blocks specifically for the histological assessment of the local spread of tumour.

A further attempt to address the issue of known residual tumour was made in 1977 by the American Joint Committee for Cancer Staging and End Results Reporting (AJCC) when it created an R classification for use as an addition to pTNM staging when there was residual tumour after definitive surgery.[4] The R classification had three subdivisions: R0, no residual tumour; R1, microscopic residual tumour; R2, macroscopic residual tumour. This was followed by the publication of survival studies in 1980 and 1981 which included information confirming the prognostic importance of separately classifying cases with known residual tumour.[5,6] In Hermanek's series, patients with local residual tumour were combined as R1/R2.[5] In the second series the only criterion for local residual tumour was histological confirmation of tumour in a line of resection.[6] In a subsequent study on the latter series, no significant difference in survival was found between patients whose residual tumour was in a line of resection only and those who had distant metastasis.[7]

Subsequently, publications by the Union Internationale Contre le Cancer (UICC)[8] and the AJCC[9] redefined the R classification to include both local and distant residual tumour while continuing the distinction between macroscopic and microscopic residual tumour. The redefined R2 included only macroscopic residual tumour (locally or distant

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metastasis) and R1 included only local microscopic residual tumour.

In 1991 an international working party report on clinicopathological staging of colorectal cancer noted that the R classification should be obligatory when using pTNM staging.[10] This was followed in 1999 by a College of American Pathologists consensus statement recommending that the surgical margin status always be reported on and, if positive, the symbol R1 be used for microscopic residual tumour and R2 for macroscopic tumour.[11]

In 2014 The Royal College of Pathologists (RCP) recommended that R1 be applied to tumours in which there is only microscopic involvement of the 1 mm circumferential resection margin. R2 was to be applied to tumours with macroscopic involvement of this margin but was also applied to cases with biopsy positive distant metastasis, regardless of the primary tumour resection margins.[12] Thus, when an R2 classification is made because of distant metastasis, a separate statement on the status of the primary tumour resection margin is necessary. The most recent AJCC recommendations continue to apply R1 to microscopic local residual tumour at the primary cancer site or regional lymph node sites while R2 applies to macroscopic tumour at the primary cancer site or regional lymph nodes but not to metastatic disease identified but not resected.[13] Therefore, current R2 classifications used by the RCP and the AJCC differ in that the former applies to either distant metastasis or macroscopic involvement of the resection margin whereas the latter refers only to macroscopic local residual tumour. In both cases the R designation remains separate from pTNM staging but may be used to supplement it.

It is apparent that the literature has become complicated by the various definitions of local residual tumour after resection of CRC and changes to these definitions over time and that no consensus has been reached. The aim of this study was to evaluate the prognostic importance of histologically verified tumour in any line of resection in the CRC specimen in relation to pTNM stages and to demonstrate how this concept may be integrated into pTNM staging to readily differentiate non-curative from potentially curative resections without the need for the separate R status classification.

METHODS

Data were drawn from a prospective database of consecutive CRC resections which was initiated at Concord Hospital, Sydney, in 1971 and contains detailed clinical, operative, pathology, adjuvant therapy and follow-up information.[14] This database had the approval of the Sydney Local Health District Ethics Committee (CH62/62011-136-P Chapuis HREC/11/CRGH206) and all patients gave written consent for the use of their data and tumour specimens for research. All resections were performed by specialist colorectal surgeons using a standardised technique.[15,16] An urgent operation refers to patients who presented with a tumour-related complication such as obstruction, perforation or haemorrhage that required an unscheduled operation. An urgent resection refers to a resection performed at an urgent operation. Resections between 1995 (before which, recurrence was recorded only for rectal cancer) and 2010 inclusive were selected for analysis and all non-deceased patients were followed for at least 5 years, apart from a small number lost within 5 years. Resections performed by members of the Concord Department of Colorectal Surgery at other hospitals with which they were associated were also included in the database. Patients were excluded if they had a non-invasive tumour, previous CRC, subsequent resection for recurrent CRC, inflammatory bowel disease, familial adenomatous polyposis coli, distant metastasis resected subsequent to the primary resection, and unknown cause of death (because cause of death is necessary for competing risks analysis).

Reporting of the resected specimen was performed by Concord Hospital pathologists with a special interest in CRC and followed a standard, detailed protocol which has been applied since the initiation of the database in 1971.[6,17] Only adenocarcinomas (including mucinous and signet ring carcinomas) were included in the database. Where multiple tumours were present, details of only the most advanced-stage lesion were included. Tumour size was measured as the greatest luminal dimension and dichotomised at the median as <4.5 versus ≥4.5 cm. Blocks were taken to demonstrate the maximum depth of direct tumour spread. Blocks were also selected to demonstrate the relationship of tumour to any line of resection where there was a possibility of involvement. Tumour in a line of resection (TLR) was defined as tumour demonstrated histologically in any deep (circumferential in lower rectum), proximal or distal resection line. Additional blocks were taken to demonstrate the infiltration of tumour into any adjacent structure or tissue[18] as well as extension to any free serosal surface.[19] An apical node was defined as the most proximal node found within 1 cm of the vessel ligation at the apex of a vascular pedicle.[20] Venous invasion, assessed by haematoxylin and eosin (H&E) staining, was recorded as involvement of thick or thin-walled veins, either within or beyond the bowel wall.[21] When doubt existed as to whether a structure involved was a vein, a negative finding was recorded. Tumour grade was classified as high grade or other depending on the degree of differentiation and anaplasia, the nature of the tumour margin (pushing or infiltrating) and the presence of small vessel invasion. Tumours were staged according to the UICC/AJCC pTNM system: stage I, tumour spread not beyond muscularis propria, no metastases; stage II, spread beyond muscularis propria, no metastases; stage III, lymph node metastases present, no distant metastasis; stage IV, distant metastases present.[22] The components of stage (local direct spread, nodal metastasis, distant metastasis) rather than the stage itself were used in analyses. All pathology features analysed were sought in every specimen and their presence or absence recorded explicitly. There were no missing data on any variable.

Patients without distant metastasis but with clinically suspected locally advanced rectal cancer identified by either preoperative magnetic resonance imaging (MRI) scan or endorectal ultrasonography were considered for neoadjuvant radiotherapy with or without complementary chemotherapy. Postoperative chemotherapy, either adjuvant or palliative and 5FU-based for the most part, was applied selectively.

The primary outcome variables were the competing risks incidence of CRC recurrence and CRC-specific death. Recurrence was defined as clinically or radiologically suspected or biopsy proven tumour in the pelvis, perineal scar or peritoneal cavity, or newly diagnosed distant metastasis. Patients were seen at least 6 monthly for the first 2 years after resection and yearly thereafter until death or 31 December 2015. Surveillance included clinical examination, sigmoidoscopy, chest X-ray and serial carcinoembryonic antigen (CEA) measurements. For rectal cancer, a computed tomography (CT) scan was performed annually as well as either sigmoidoscopy or colonoscopy after restorative operation. For colon cancer, colonoscopy was generally repeated between 3 and 5 years following resection. The occurrence, date and cause of death were ascertained principally from the patient's surgeon or family physician or hospital records; from a close relative if necessary; or, in a small number of cases, from the national death registration system.

Statistical analysis

The statistical significance of differences between percentages was evaluated by the chi-squared test. For recurrence after potentially curative resection, we used competing risks methods rather than naïve Kaplan–Meier estimation[23] or recurrence-free survival, because the former over-estimates the probability of recurrence due to violation of the assumption of independence of censoring,[24,25] while the latter cannot separate failure due to recurrence from failure due to causes other than CRC.[26] The latter is also the explanation for our use of competing risks methods to estimate the incidence of CRC-specific death for both curative and non-curative resections. In competing risks analyses the terminal events were recurrence at any site or CRC-specific death, with non-CRC death as a competing risk for these outcomes. The date of resection was the starting point for follow-up times, which were censored at last contact for patients who did not experience the terminal event and were either lost to follow-up or remained alive in December 2015. All patient and tumour covariates that were not natural binary variables were dichotomised at conventional or appropriate cutting points to simplify comparisons of effect

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