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Histopathological regression grading versus staging of rectal cancer following radiotherapy

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Summary

Aims: To compare histological grading of rectal cancer radiotherapy response with pathological staging as a prognostic indicator.

Methods: Histological tumour regression was five tier graded in 102 rectal cancer patients treated with preoperative radiotherapy [short course ($n=34$), long course ($n=68$)]. Differences between these grades and between the two radiotherapy regimes were assessed. These variables, pTMN staging and others were correlated with relapse free survival at 3 years.

Results: 22 patients suffered disease recurrence and four died during a mean post-operative follow-up of 40.3 months. There were 52 good responders (tumour regression grades 1–3) and 50 poor responders (tumour regression grades 4–5). Regression was greater following the long course regime ($p<0.0001$). Otherwise, there were no significant differences between the response groups and between the two regimes, including the number of lymph nodes found in the resected bowel. Only the pN status correlated with relapse free survival on multivariate analysis ($p=0.0004$; HR $=4.26$, 95%CI $=1.66-10.93$ for pN2 versus pN0).

Conclusions: The number of lymph nodes found for staging was not influenced by either the extent of primary tumour regression or the type of radiotherapy. pN status, but not tumour regression grade, is a reliable predictor of survival.

Key words: Radiotherapy response, rectal cancer, staging, tumour regression grading.

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INTRODUCTION

As a group, rectal cancer patients benefit from preoperative radiotherapy (DXT) with reduced local recurrence rates following surgery, although whether this translates to an improved overall survival is less clear.[1–3] Part of the reason for this may lie in the variations seen in the degree of DXT response within equally treated rectal cancers. Thus, an interest is gathering in incorporating the histological estimate of the extent of DXT induced tumour regression into the current standard pathological assessment of the resected bowel. Such regression grade has been shown to relate to patient survival in several cohorts.[4–7]

But does tumour regression grading offer any advantages over the traditional pTNM staging, with which we are already familiar as a robust reliable predictor of patient outcome? Furthermore, implementing this at a routine level will firstly require the resolution of issues regarding standardisation and definitions. As applied to rectal cancer, various such grading systems have been reported in the literature. These have in common the quantitative or semi-quantitative assessment of the microscopic volume of tumour loss as the essential criterion, but differ in their name [e.g. tumour regression grade (TRG, which will be used in this study),[8,9] grade of regression,[10] rectal cancer regression grade,[11] residual tumour cell density[12] and grade of pathological response[13]], nomenclature, cut-offs between the grades within each system, and the opinions as to the ideal number of tiers that should be applied (e.g. 3,[9,11,12] 4[13] or 5[8,10]).

At a practical level, estimating the volume of tumour loss requires an approximation of the extent of the initial tumour. The latter can be difficult to ascertain, especially as tumour induced desmoplasia overlaps morphologically with fibrosis that replaces areas of DXT induced tumour death.

Despite these reservations, grading the tumour response to preoperative radiotherapy would be an ideal approach to prognostication in these patients, if it can be proven to be superior to the pTNM staging. To investigate this, and to highlight any potential pitfalls of tumour regression grading, we examined these factors and compared them to early local recurrence and death rates in a cohort of 102 patients.

MATERIALS AND METHODS

Data were collected retrospectively from the Departments of Radiation Oncology, Anatomical Pathology and Colorectal Surgery at the Royal Prince Alfred Hospital (RPA), Sydney, Australia, through review of patient databases and histological slides. All patients were diagnosed and treated by the various visiting and staff specialists of the aforementioned departments. This study received relevant ethics approval from the Sydney South West Area Health Service Human Research Ethics Committee.

Patient selection

A total of 136 cases of rectal cancer treated with preoperative DXT were identified from 1998 to 2007. Of these, 34 cases were excluded for the following reasons (Fig. 1): (1) treated cancer was a local recurrence, rather than a primary tumour ($n=13$); (2) DXT was of palliative intent ($n=12$); (3) subsequent surgical resection and follow-up were conducted elsewhere ($n=8$); (4) treated cancer was not an adenocarcinoma ($n=1$ melanoma of anorectal junction).

The remaining 102 patients were included in the study, each of whom received curative treatment at RPA for a locally advanced (at least cT3) primary

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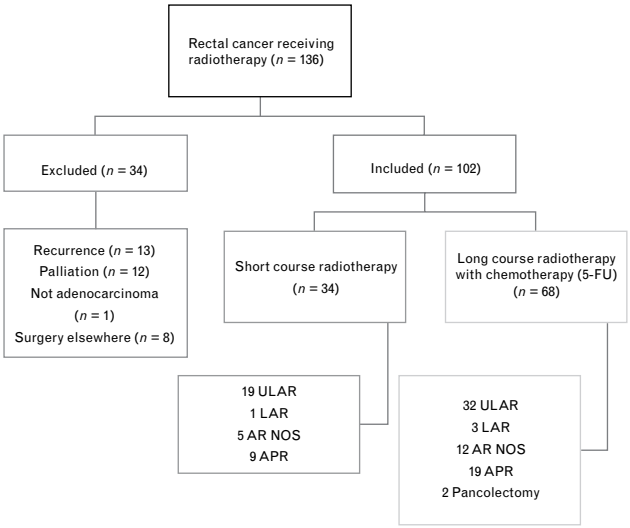

Fig. 1 Patient selection and treatment. 5-FU, 5-fluorouracil; APR, abdomino-perineal resection; AR NOS, anterior resection, not otherwise specified; LAR, low anterior resection; ULAR, ultralow anterior resection.

rectal adenocarcinoma. Stratification of patients into either of the two DXT regimes and ensuing surgery types (see below) were based on consideration of each patient's clinical and radiological disease extent and relative urgency for surgical intervention.

Preoperative DXT

Thirty-four patients received short course radiotherapy (SCR), consisting of 25 Gy in 5 fractions (i.e., 5×5 Gy) over 1 week with surgical resection of irradiated tumour performed in the following week. The remaining 68 patients received conventional long course radiotherapy with chemotherapy (LCRC), consisting of 50.4 Gy in 28 fractions (i.e., 28×1.8 Gy) over 5 weeks with (in all but one patient) continuous infusion of 5-fluorouracil over the first and last weeks. Subsequent surgical resection occurred between 4 and 6 weeks following the completion of LCRC.

Surgery

Curative operative procedures for the irradiated rectal cancers included ultra-low anterior resection (19 SCR, 32 LCRC), low-anterior resection (1 SCR, 3 LCRC), anterior resection not otherwise specified (5 SCR, 12 LCRC), abdo-mino-perineal resection (9 SCR, 19 LCRC) and pancolectomy (2 LCRC). In 13 cases, various adjacent organs were also resected (4 SCR, 9 LCRC), including vagina, uterus, bladder, prostate, seminal vesicles and vas deferens.

Histopathology

All resected large bowel were evaluated histologically and reported in a standardised synoptic format that included the following variables. If any of these variables were missing in the original report, one of the authors (J-SS) reviewed the microscopic slides and assessed them as per the criteria outlined below.

Tumour regression grade (TRG)

This five tier grading system was initially described by Mandard *et al.*[8] for the evaluation of the extent of chemoradiotherapy (CDXT) response in oesophageal cancer, then subsequently demonstrated by others as applicable to rectal cancer in the same context.[14,15] The grades are specified as: (1) complete regression with fibrosis only, no residual tumour seen; (2) rare residual single cells or small aggregates of tumour scattered amongst fibrosis; (3) residual large aggregates of tumour present, but fibrosis still predominates; (4) abundant residual tumour outgrowing fibrosis; and (5) tumour without regression.

Differentiation grade

The standard three tier grading (well, moderate and poor) was applied. In cases where the tumour grade was reported as a spectrum (e.g., moderate to poor) in the original report, the slides were reviewed and an overall grade was assigned as that applicable to the worst area within the given tumour. As per the World Health Organization (WHO) classification of tumours of the digestive system,[16] all mucinous adenocarcinomas were graded as reflecting poor differentiation.

Stage

The individual reports quoted either the pathological (p)TNM or the Australian clinico-pathological (ACP) staging.[17] The latter cases were reviewed and the staging converted to the pTNM format in accordance with the 2002 version of the American Joint Committee on Cancer guidelines.[18] Though similar, ACP stage differs from the pTNM counterpart in taking into account both the apical node involvement and positive surgical margin, while making no distinction in the number of regional lymph nodes involved by metastasis or in the local extent of disease beyond the rectal muscularis propria (where an enveloping free serosal surface is absent).

Other variables

Both the total number of lymph nodes retrieved from dissection of the included meso-rectum and -colon, as well as those involved with metastases were recorded.

Follow-up

The patients were followed up at outpatient visits by the respective colorectal surgeon with various clinico-radiological (including physical examination, colonoscopy and computed tomography) and biochemical (including serum carcinoembryonic antigen level) modalities. Relapse-free survival (RFS, at 3 years), a sensitive early end point in survival analysis,[19] was defined as time from the date of surgery to the date of first recurrence/relapse (local or distant) or death from any cause, excluding as events any second primary cancers.

Statistical analysis

Data were analysed using SAS v8 (SAS Institute, USA) and GraphPad Prism v5 (GraphPad Software, USA). Prior to analysis, age and number of lymph nodes were dichotomised around the median. TRG (1–3 versus 4–5), pT status (0–2 versus 3–4) and pTNM (I–II versus III–IV) were also dichotomised. Differences between groups were determined using the chi-squared test for categorical variables, and Student *t*-test and analysis of variance for continuous variables.

Survival rates and survival curves were derived from the Kaplan-Meier procedure and the log-rank test was used to compare survival curves. Variables with a p value <0.25 in single variable Cox regression models were all initially included in the multivariate model, from which the final model was determined by backward elimination of variables. Survival time was as defined above (RFS, see 'Follow-up' under 'Methods'). The proportional hazards assumption was tested using time dependent variables in the Cox regression models. The final model satisfied the proportional hazards assumption. Results from the Cox regression models were reported as the hazard ratio (HR) with associated 95% confidence intervals (95%CI). A p value of less than 0.05 denoted statistical significance.

RESULTS

General patient and pathological characteristics

The median age of the 102 patients was 63 years (range 31–85 years), with 70 males and 32 females. As expected in a cohort treated for curative intent, none of the cases showed pathological evidence of distant metastasis (i.e., $pM = 0$) upon examination of the resected specimens, which consequently equated to a lack of stage IV patients in our analysis.

Furthermore, no residual tumour was seen in four of the cases following neoadjuvant therapy, as indicated by TRG of 1 (Table 1). In each of these four cases, not only the pT but also the pN were 0. Consequently, no differentiation grade or pTNM stage were assigned to these four cases. The remaining cases showed a spectrum of TRGs, as listed in Table 1. Given the small number of cases in each TRG category, and in line with other similar studies (see Discussion),[6,20] the TRG was subsequently dichotomised into ranges 1–3 and 4–5 to divide the cohort into good ($n = 52$) and poor ($n = 50$) response groups, respectively.

Up to 33 lymph nodes were examined in the resected bowel from each patient (mean = 11.6; median = 10). Interestingly, the number of lymph nodes found for this purpose was not influenced by either the extent of primary tumour regression or