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Review

A meta-analysis assessing the survival implications of subclassifying T3 rectal tumours

M.R.S. Siddiqui [a,b], C. Simillis [c], J. Bhoday [a,b], N.J. Battersby [b], J. Mok [a], S. Rasheed [c], P. Tekkis [c], A.M. Abulafi [a], G. Brown [c,*]

[a] Department of Colorectal Surgery, Croydon University Hospital, Croydon, Surrey, CR77YE, UK
[b] Department of Radiology, Royal Marsden Hospital, Sutton, Surrey, SM2 5PT, UK
[c] Department of Surgery, Royal Marsden Hospital, Fulham Rd, London, SW3 6JJ, UK

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Abstract ***Aim:*** Although T3 tumour subclassifications have been linked to prognosis, its mandatory adoption in histopathological reports has not been incorporated. This article focusses on the survival outcomes in patients with T3 rectal cancer according to extramural spread beyond the muscularis propria.

Methods: A systematic review of all studies up to January 2016, without language restriction, was identified from MEDLINE, Cochrane Controlled Trials Register (1960–2016) and Embase (1991–2016). All studies reporting on survival and T3 tumours with a defined cut-off of 5 mm ± 1 mm tumour invasion beyond the muscularis propria for rectal cancers were included. Hazard ratios were extracted directly from the studies or from survival curves using the technique described by Parmar. Quality assessment was performed using the Newcastle-Ottawa scale.

Results: Tumours with invasion more than 5 ± 1 mm from the muscularis propria had statistically significantly worse overall survival (natural log of the hazard ratio [lnHR]: 1.40 [1.06, 2.04], $p < 0.001$) and there was no statistically significant heterogeneity ($\chi^2 = 1.541$, df = 3, $p = 0.673$, $I^2 = 0$). There was statistically significantly worse disease-free survival in more invasive tumours (lnHR: 1.49 [1.19, 2.00], $p < 0.001$) and cancer specific survival (lnHR: 1.22 [0.917, 1.838], $p < 0.001$). Overall survival in patients who had preoperative therapy was higher in patients with less invasion beyond the muscularis propria [$p < 0.01$].

Conclusions: Subclassifying all T3 rectal tumours according to the depth of spread with a cut-off of 5±1 mm beyond the muscularis propria is prognostically relevant for overall

* *Corresponding author*: Department of Radiology, Royal Marsden Hospital, Downs Rd, Sutton, Surrey, SM2 5PT, UK. Fax: +208 643 9414.
E-mail address: Gina.Brown@rmh.nhs.uk (G. Brown).

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survival, disease-free survival and cancer-specific survival irrespective of the nodal status; therefore, subclassifying T3 tumours should be a reporting requirement in histopathology reports.

1. Introduction

Staging of rectal cancer facilitates more targeted treatment strategies. Formal staging systems have undergone significant changes within the last 100 years. Originally described in 1926, Lockhart-Mummery formally categorised his series of rectal tumours into A (growth that has not invaded the muscular coat), B (involvement of the muscular coat but no involvement of the surrounding glands) or C (involvement of the surrounding glands). These categories were based on the degree of tumour invasion seen at the time of surgery, with C being the most invasive [1]. Subsequent staging systems expanded and incorporated histological considerations to the original descriptions. One of the most well-known staging classifications was developed by Sir Cuthbert Dukes in 1932, further refined in 1935 with other colleagues [2,3]. The Dukes staging was validated in 1958 and reported 5-year survival of 98%, 78% and 32% in patients with Dukes A, B and C tumour staging, respectively [4]. These historical categories can be broadly mapped to the current UICC/AJCC tumour-node-metastasis (TNM) staging system.

The UICC/AJCC TNM scale [5,6] categorises rectal tumours into five prognostic groups based on different combinations of tumour invasion, nodal involvement and metastases. Stage 0 of the TNM classification is considered a tumour *in situ* and carries a good prognosis; stage I rectal cancer has a 5-year relative survival of 87%. Prognosis worsens with higher stages, and 5-year relative survival is only 12% in patients with stage IV (metastatic) disease [7].

AJCC staging manuals regard T3 tumours as a single group and define them as invasion of tumour through the muscularis propria into the subserosa, non-peritonealised pericolic or perirectal tissues. In 1993, the supplement to the 4th edition of the TNM manual proposed an optional tumour subclassification because of reports of better prognosis in more invasive T3 tumours; however, this has not been adopted [8,9]. This subclassification was dependent on invasion beyond the muscularis propria and was divided into four groups: T3a (<1 mm), T3b (1–5 mm), T3c (5–15 mm) and T3d (>15 mm). Despite evidence that these subdivisions correlated with outcomes, application of these divisions to staging was still perceived to be controversial.

The lack of adoption was based on the findings of a working party report of staging systems [10]. The working party cited the CONCORD study as evidence to suggest that there was a difference in opinion regarding subclassifications of T3 tumours [11]. However, using the CONCORD study to support a controversial view of T3 subclassifications does not accurately reflect the methodology nor the findings of the CONCORD study [11]. The CONCORD study investigated a combined cohort of colonic and rectal tumours. Moreover, the researchers in the CONCORD study did not subdivide their tumour cohort according to the level of invasion beyond the muscularis propria. Their findings showed that the early cancers (stage A) could be classified in to three groups, the third of which had similar prognostic value to more invasive tumours (stage B1). The conclusion derived from this was that invasion beyond the muscularis propria as a single group was no different to the slightly more advanced early cancers. Based on other studies [8,12,13], this conclusion may well be incorrect and is more in keeping with suggestions that these B1 (T3) tumours are a heterogenous group.

Currently, the perceived controversy has ensured that T3 tumour classifications remain an optional rather than a compulsory reporting item in subsequent TNM and AJCC staging manuals.

Since 1993, when the optional reporting was first proposed, a further 12 studies have reported on T3 subclassifications in rectal cancer [8,9,12–21]. As a result of the increasing amount of data regarding T3 subclassifications and their potential importance for treatment strategies [22], an analysis of the prognostic significance would, therefore, be relevant.

This meta-analysis will help answer the aforementioned question to see if the 'optional' status of T3 subclassification needs to be revisited. This answer will be achieved by focussing on the survival outcomes in patients with T3 rectal cancer with greater or less than 5±1 mm invasion beyond the muscularis propria.

2. Methods

2.1. Protocol and registration

The title, methods and outcome measures were stipulated in advance, and the protocol is available in the PROSPERO database [23].