

Original Article

The Reliability of Lymph-node Staging in Rectal Cancer After Preoperative Chemoradiotherapy

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ABSTRACT:

Aims: To determine the prognostic significance of the nodal stage and number of nodes recovered in the surgical specimen after preoperative synchronous chemoradiation (SCRT) and surgery for locally advanced or unresectable rectal cancer.

Materials and Methods: One hundred and eighty-two consecutive patients with locally advanced or unresectable (T3/T4) rectal carcinomas were entered on a prospective database and treated in this department with preoperative chemoradiation, followed 6–12 weeks later by surgical resection. Most patients received chemotherapy in the form of low-dose folinic acid and 5-fluorouracil (5-FU) 350 mg/m² via a 60-min infusion on days 1–5 and 29–33 of a course of pelvic radiotherapy delivered at a dose of 45 Gy in 25 fractions over 33 days to a planned volume. After resection, patients with a positive circumferential margin (≤ 1 mm), extranodal deposits or Dukes' C histology received adjuvant 5-FU-based-chemotherapy ($n = 40$).

Results: After SCRT, 161 patients underwent resection. Twenty-one patients remained unresectable or refused an exenterative operation. Median follow-up is 36 months. Down-staging was achieved in most patients, with 19 having a complete pathological response (pT0). The median number of lymph nodes recovered for all patients was five (range 0–21). The 3-year survival rate for node-positive patients is 47%, for node-negative patients with less than three lymph nodes recovered is 62% and for node-negative patients with three or more lymph nodes recovered is 70%. Compared with node-positive patients, simple regression models revealed a reduced hazard ratio (HR) of 0.72 (0.36–1.43) for node-negative patients with less than three nodes recovered and 0.48 (0.26–0.89) for node-negative patients with three or more lymph nodes recovered. In a multivariate model, including nodal status, excision status, age and sex only positive excision margins significantly predicted a poor outcome: HR = 3.05 (1.55–5.97).

Conclusions: The number of nodes found after preoperative chemoradiation is a significant prognostic factor by univariate analysis. In this study, patients with node-negative histology, and at least three nodes recovered, had better long-term survival than patients in whom two or less nodes were recovered or with positive nodes. This effect was attenuated by the inclusion of excision status in multivariate models. Beresford, M. *et al.* (2005). *Clinical Oncology* 17, 448–455

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Key words: Chemoradiation, lymph nodes, rectal adenocarcinoma

Received: 20 January 2005 Revised: 12 April 2005 Accepted: 17 May 2005

Introduction

About 12 000 people in the UK develop rectal cancer each year. The optimal management of stage II and III rectal cancer remains an increasing challenge for oncologists.

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Although surgery remains the mainstay of treatment, historically a high risk of local recurrence and poor survival has been reported for these patients. Randomised studies in the era before total mesorectal excision show that 5-year survival rates for rectal cancer were about 60% for Duke's B2 and only 25% for Duke's C [1]. Five-year survival rates remain in the region of 40–55% in most series when patients have had a curative resection.

The main prognostic factors remain: the extent of the primary tumour (T stage), regional lymph-node status

(N stage) and whether there is sufficient (>1 mm) circumferential resection margin. Postoperatively, tumours with an unfavourable prognosis (and hence suitable for adjuvant chemotherapy) can be selected on the basis of pathological findings, such as a histologically involved circumferential margin, poor differentiation, vascular invasion, invasion into the perirectal fat, involvement of the peritoneal surface or other organs (T4 status) and lymph-node status [2–5]. Unfortunately, all these features may be altered or effaced by preoperative chemoradiation.

The patients at highest risk of disease recurrence need to be identified to offer further adjuvant treatment. Traditionally, the major discriminating factor has been the presence or absence of involved regional lymph nodes. The standard of lymph-node examination in the resection specimen as a determinant of prognosis was set when the treatment for rectal cancer was primary surgery followed by adjuvant radiotherapy, chemotherapy, or both. Although evidence from the Dutch TME study concludes that short-term preoperative radiotherapy does not contribute to down-staging if the interval is less than 10 days, the lymph nodes examined were fewer in number in those who received preoperative radiotherapy — a mean of 7.7 compared with 9.7 in those treated with surgery alone [6]. However, the down-staging effects of preoperative neoadjuvant chemoradiotherapy may completely efface nodal disease present at initial staging. Post-chemoradiation nodal status may therefore be a less reliable indicator of future outcome.

Methods of identifying which patients may benefit from preoperative synchronous chemoradiation (SCRT) include digital rectal examination (DRE) and cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) by an experienced coloproctologist can identify fixity as an indicator of locally advanced disease. Pelvic MRI using a surface phased array coil can demonstrate the relationship of the primary tumour to the mesorectum and the surrounding mesorectal fascia, and is increasingly used as a method of selection of patients for SCRT.

Thus, preoperative SCRT is increasingly offered to patients with rectal cancer who are expected on MRI criteria to have a close or involved resection margin with current surgical techniques [7]. Histological examination of the specimens has confirmed high rates of complete pathological response (10–30%). Neoadjuvant treatment has been shown to downstage tumours, with more cases of Dukes' A staging, a better resection rate and more sphincter-sparing procedures [8,9]. Whether this correlates with an improved survival remains controversial [10,11]. However, all groups agree that after chemoradiation, less lymph nodes are recovered in the surgical specimen. Searching for lymph nodes in a specimen is tedious and laborious, particularly after SCRT, and a small sized node can easily be missed.

A diagnosis of a lymph node negative tumour should suggest a good prognosis, but outcomes for Dukes' B cancers are extremely variable. This is likely to be due to under staging caused, at least in part, by insufficient lymph-node recovery. Some attempts have been made to define

a minimum number of lymph nodes needed in the resection specimen to be able to confidently call a tumour node negative. For colorectal cancer as a whole, the International Union Against Cancer (UICC) requires at least 12 cancer-negative nodes in the specimen [12]. Others have suggested that finding seven negative nodes would give a 95% certainty that the tumour was in fact a Dukes' B, and it certainly seems to be the case that if fewer than seven nodes are recovered, those categorised as Dukes' B have much poorer outcomes [13,14]. This information comes from patients who have not received preoperative treatment, and there are currently no good data on how many nodes should be examined to reliably exclude nodal involvement after SCRT.

It is clear that down-staging after preoperative SCRT is a significant prognostic factor, and that patients with pT0, T1 or T2 disease have an excellent prognosis, whereas those with T3, T4 or node-positive disease fare less well and may benefit from further adjuvant chemotherapy [15].

The aim of this study is to determine whether the number of nodes found and examined histologically after SCRT determines the clinical outcome, and hence to identify a minimum number of lymph nodes needed after preoperative SCRT to confidently predict the stage of rectal cancer and indicate any need for further adjuvant therapy.

Material and Methods

The Mount Vernon Cancer Centre serves a population of 1.8 million. A prospective database confirms that 182 consecutive patients with primary rectal cancer considered unresectable by the referring surgeons received SCRT between January 1995 and December 2002. One hundred and sixty-one patients proceeded to surgical resection after the neoadjuvant treatment. (Fig. 1).

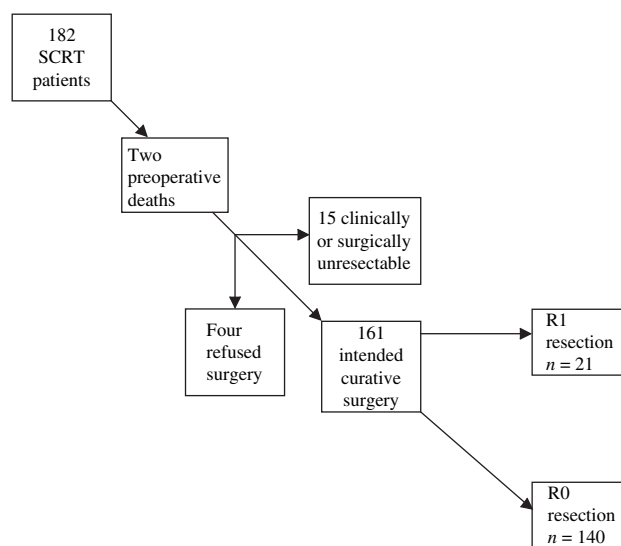


Fig. 1 – Patients in present study.

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