

# Recurrence of rectal cancer: a study on patients with rectal cancer referred to Sir Paul Boffa Hospital during 2001-2003

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## Abstract

Surgery is the mainstay of treatment of rectal cancer. One third of all treatment failures are secondary to local recurrence usually leading to a painful and distressing death. Radiotherapy has been shown to decrease local recurrence rates and overall survival. The results of a local retrospective study are discussed, identifying and describing the recurrence rates in rectal cancer. Our management pathways are also reviewed and compared to current evidence-based medicine and published clinical trials.

## Introduction

The management of rectal cancer has undergone marked changes in the last twenty years leading to improved results in local and distant recurrence rates and overall survival. These changes have occurred in the staging, surgical management, histological evaluation, radiotherapy and chemotherapy of the condition. We have carried out an audit of patients with Duke's B and C rectal cancer referred to the Oncology Department in the years 2001 to 2003 to evaluate local and distant recurrence rates and to examine ways in which we can improve our results.

## Keywords

Rectal Cancer, Radiotherapy, Recurrence

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## Methodology

One hundred and five patients with rectal cancer were referred to the oncology department between the years 2001 to 2003 inclusive. Of these 68 patients were Duke's stage B and Duke's stage C the remainder being either Duke's stage A or Duke's stage D. These were the only patients eligible for adjuvant treatment, since this is not indicated in the management of Duke's A or Duke's D.

Of those 68 patients, 35 were Duke's Stage B and 33 Stage C. Records have been traced on 57 patients out of 68 patients, 30 with Duke's B and 27 with Duke's C. These 57 patients constitute the population for this audit, which is aimed at trying to improve our results by changing our practice.

The records of 11 of these 68 patients could not be traced and therefore they were not included in the study. The histology report of 9 of these patients was traced and 3 are known to have been Duke's stage B and 6 are known to have been stage Duke's stage C. Also, of these eleven patients staged B and C, where records were not traced, 7 are known to be dead. However, the cause of death obtained from tracing records of the patients' death certificate does not specify if these patients developed a recurrence of the disease or not. Also, the accuracy of such data is questionable. The lack of complete records almost certainly introduces bias to our findings. This means that our results for the whole group are likely to be worse than in the 57 patients whose records are complete. Nonetheless the study remains a useful exercise in the ultimate aim of improving our practice.

## Results

Twenty three per cent of Duke's B and 7.4% of Duke's C patients suffered a local recurrence by the time of the audit (June 2007) and 20% of Duke's B and 14.8% of Duke's C suffered a distant recurrence at the time of first relapse. One patient with Duke's C (3.7%) suffered both a local and distant recurrence. The overall recurrence rate for Duke's B was 43% and for Duke's C 25.9% (figure 1).

Figure 2 gives a breakdown of treatment received by all Duke's B and C patients referred. Seventy six per cent of Duke's B patients received radiotherapy only, 4% chemotherapy only and 16% both chemotherapy and radiotherapy. Four per cent of Duke's B patients received no further treatment. Sixty-eight per cent of patients with Duke's C rectal cancer received radiotherapy and chemotherapy, 29 % received radiotherapy alone and 3% chemotherapy only.

Figures 3 and 4 illustrate the type of post-operative treatment received by patients, who eventually developed a recurrence. The majority of Duke's B patients received post-operative radiotherapy, with only one having received pre-operative radiotherapy.

All patients underwent complete resection of the tumour either a low anterior resection or an abdominoperineal resection. Chemotherapy consisted of weekly 5-Fluorouracil and folinic acid.

## Discussion

The management of rectal cancer, once this has been diagnosed, starts with adequate staging to determine the optimal treatment for each individual patient. The use of endorectal ultrasound, CT Scanning and MRI Scanning allows much more accurate determination of T stage, nodal involvement and distant metastasis (TNM).

Endorectal ultrasound provides the most accurate method of assessing depth of bowel wall invasion for early tumours i.e. T<sub>1</sub> and T<sub>2</sub> tumours but is less useful for tumours extending beyond this.<sup>1</sup> It is also operator dependent to a greater extent than CT and MRI. To assess the risk of involvement of the mesorectal excision plane and therefore the risk of local recurrence MRI is the preferred modality of imaging especially MRI with a phased array coil.<sup>2</sup>

CT Scanning is still the modality of choice for assessing distant spread and modern multi-slice CT would allow distant and local staging in a single investigation. A 4–16 slice CT is satisfactory for high rectal tumours with a wide circumferential resection margin, which are at low risk of recurrence but inadequate for low rectal tumours especially in less experienced hands. The newer 64–128 slice CT Scans may well alter this scenario.<sup>3</sup>

For the assessment of nodal involvement, CT is generally unsatisfactory. Endorectal Ultrasound is very useful especially for guiding fine needle aspiration but the latter technique though highly accurate is not widely used. MR with new contrast agents is the investigation of choice for assessing pelvic node involvement. FDG – PET has so far been disappointing in detecting the low volume nodal disease usually seen in rectal cancer.

It is now clearly established that the type of operation carried out (quality of the surgery) has a major impact on local recurrence rates and ultimately survival.<sup>4</sup> The introduction of total mesorectal excision (TME) has been accompanied by a marked reduction in local recurrence rates. This procedure involves a longer operation with an increased complication rate but produces a local recurrence rate in “curative” surgery of around 4% at 5 years and overall recurrence rate of around 18%.<sup>5,6</sup> The best reported results from the North Central Cancer Treatment Group for resectable tumours with conventional surgery (i.e. non TME) plus radiotherapy or combined chemo radiation for local recurrence are 25% and 13.5% respectively at 5 years and 62.7% and 41.5% for overall recurrence.

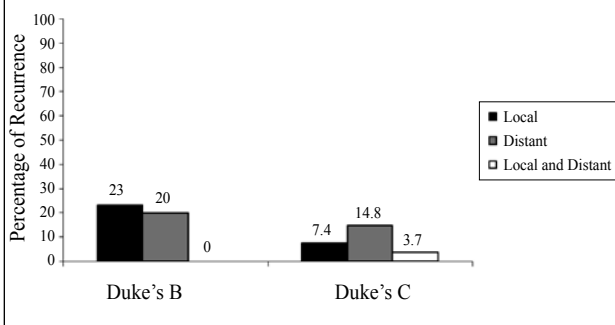
The results from TME have been replicated in a number of centres and indicate that the poorer results of conventional surgery cannot be compensated for by radiation or chemo radiation. For tumour in the middle or distal rectum TME is always indicated.

The pathologist too has an important role to play in improving results in the management of rectal cancer. The pathologist's report serves as an important audit of surgical technique and guides the selection of patients for post-operative adjuvant treatment. The radiologist's report should guide the selection of patients for pre-operative treatment.

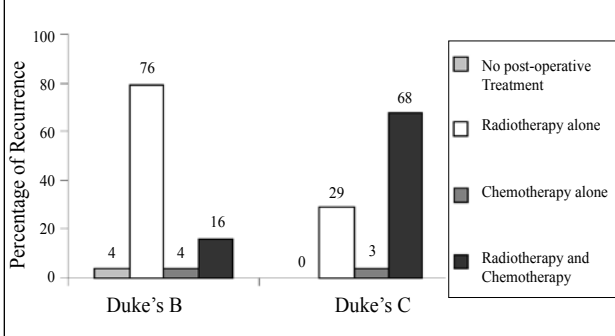
For many years it has been standard local practice to operate patients with rectal cancer and refer them post-operatively to the oncology department. This has the advantage of allowing more accurate staging, an advantage that should be largely eliminated by using optimal staging imaging pre-operatively. It has the disadvantage of denying patients pre-operative radiotherapy or chemo radiation.

There is now a consensus based on several clinical trials that pre-operative radiotherapy decreases the local recurrence rate even if the operative procedure is a TME.<sup>7</sup> A meta-analysis of 14 randomised controlled trials showed that pre-operative radiotherapy significantly improves survival and 5 year cancer specific survival with marked reductions in local recurrence rates.<sup>8</sup> It is also clearly established that pre-operative

**Figure 1:** Percentage of Recurrence in patients with Duke's B and Duke's C Rectal Adenocarcinoma



**Figure 2:** Treatment of patients with Duke's B and C rectal



radiotherapy offers superior results when compared to post-operative radiation as well as decreased toxicity. No trial of post-operative radiation has shown a survival advantage.

If the circumferential resection margin is not threatened and the tumour is not too distal, a short 5 day course of pelvic radiation followed one week later by surgery is effective in reducing local recurrence.

Two studies comparing pre-operative radiation versus pre-operative radiation plus 5-Fluorouracil/leucovorin pre-operative chemotherapy, showed a reduction in local recurrence rate for the chemo radiation arm without an improvement in overall survival. It is hoped that the use of chemotherapy regimens known to have higher response rates in the metastatic setting (FOLFOX/FOLFIRI) as well as improved survival in the adjuvant setting may impact on overall survival. The use of new biological therapies, such as Bevacizumab, offers similar hope.

In our series only one patient was referred pre-operatively between 2001 and 2003. Happily this practice is beginning to change with several patients with fixed inoperable tumours referred over the last few years and more recently patients with more advanced but operable tumours. For those with bulkier/fixed tumours we are using combined pelvic radiation and FOLFOX (5-Fluorouracil, leucovorin and Oxaliplatin). The protocol has considerable toxicity and is unsuitable for frail patients but is certainly manageable in fitter patients and is beginning to produce gratifying results at least in terms to tumour response. It is still too early to comment about local recurrence and overall recurrence rates. This will be the subject of a future audit.

Local recurrence of a rectal cancer is painful, causes marked morbidity and deterioration of quality of life. Treatment that can be offered is usually palliative and such a relapse therefore ultimately leads to death of the patient.

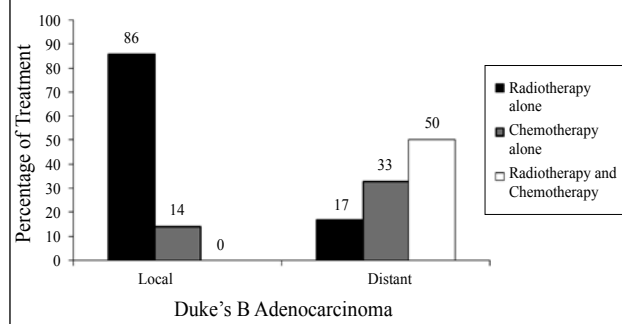
Our local recurrence rates for the years 2001 – 2003 (16% Duke's B and C) are disappointingly high compared to what can be achieved by TME alone (4% localized recurrence). The Swedish Rectal Cancer Trial reported 25% local recurrence rates with conventional surgery, reduced to 11% by short course pre-operative radiotherapy.<sup>9</sup> A Dutch Rectal Study comparing TME versus short course pre-operative RT and TME showed reduction in local recurrence rate from 8.2% for surgery alone to 2.4% for combined treatment. In our series 92% of Duke's B patients received radiotherapy, 16% receiving both chemotherapy and radiotherapy. Twenty three per cent of these suffered a local relapse. Radiotherapy in all but one patient was however delivered solely post-operatively and this is known to be less effective. The lower local relapse rate in the Duke's C group (7.4%) is counter intuitive and the distant recurrence rate (14.8%) even more so. It may reflect the higher use of chemotherapy (72%) in this group but numbers are too small to draw a conclusion. Also one should consider the possibility of understaging due to harvesting and examination of an inadequate number of nodes for our Duke's B series. TNM and NICE guidelines suggest a minimum of 12 nodes should be harvested.<sup>10</sup> The impact of adjuvant chemotherapy on

Duke's B cancer is minimal – of the order of 1–2 % reduction in overall recurrence at 5 years with 5-Fluorouracil based chemotherapy and marginally better with FOLFOX. Twenty per cent of our Duke's B patients received chemotherapy. This seems difficult to justify but must be seen in the light of unreliable staging, younger patients who would be treated more aggressively and poorly differentiated tumour. The evidence for benefit in B<sub>2</sub> tumour is controversial. Notwithstanding these figures require a review of our policies.

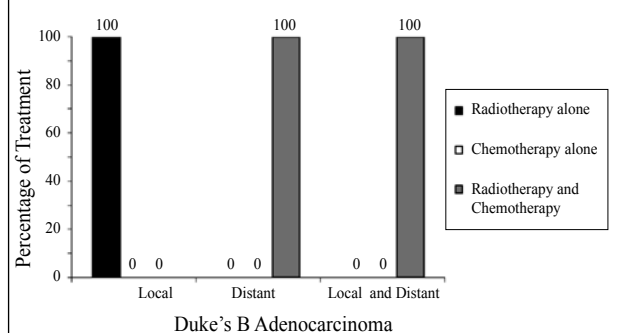
With Duke's C rectal cancer the impact of adjuvant chemotherapy is larger – around 12% absolute difference in survival at 5 years with 5-Fluorouracil based chemotherapy and 15% with FOLFOX for patients with 1–3 involved nodes. Again the difference in outcome between the two regimes barely justifies the increased toxicity and cost of FOLFOX. The benefit from chemotherapy increases the worse the prognosis, so that FOLFOX becomes justified in younger fitter patients with more than 10 nodes involved and poorly differentiated tumour (18% alive due to 5-Fluorouracil based chemotherapy versus 25% for FOLFOX at 5 years). Oxaliplatin is not available for use in the adjuvant setting in Malta's public hospitals but is widely used in metastatic disease. The new drugs oxaliplatin and irinotecan were not used at all in adjuvant treatment in the period under review.

Our figures for overall recurrence (43% Duke's B and 27.4% Duke's C) are difficult to explain but statistics in small numbers can be misleading. However, they do not compare well with the

**Figure 3:** Post-operative treatment in Duke's B who later developed a recurrence



**Figure 4:** Post-operative treatment in Duke's C who later developed a recurrence



figures of Duke's B and C combined, treated with TME alone<sup>7</sup> (18% overall recurrence). They approach more those treated by conventional surgery and radiation (63% for Duke's B and C combined) or conventional surgery and chemo radiation (41.5%). Even if the groups are not strictly comparable and our numbers are small the implication is clear, that TME has a major impact both on local and overall recurrence, pre-operative radiotherapy further reduces local recurrence, and that adjuvant chemotherapy reduces overall recurrence rate, at least in Duke's C rectal cancer.

## Conclusion

As the title indicates the audit was aimed at a review of recurrence rates of rectal cancer patients and more specifically to look at the way these patients are investigated and treated in order to come up with a protocol that will improve results.

Disease free survival (DFS) is therefore very much a point examined by the audit though overall survival (OS) was not since most distant and local recurrences are ultimately fatal.

The above data urgently call for the implementation of new protocols using appropriate imaging, referral of selected patients for pre-operative radiation or chemo radiation and finally adequate surgery, audited by a detailed and accurate pathology report.

A proposed plan of action for optimal diagnosis and management of rectal tumours is as follows:

1. Endoscopy and biopsy
2. Pelvic MRI
3. CT thorax, abdomen and pelvis to exclude distant metastasis.
4. Referral for pre-operative radiotherapy if circumferential resection margin is threatened or for fixed or bulky tumours.

5. TME is carried out for all patients with middle or low rectal tumours
6. Pathology report is to audit the adequacy of surgical technique and indicate best post-operative treatment e.g. +/- chemotherapy.

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