



Time to local recurrence as a prognostic factor in patients with rectal cancer

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Abstract

Aims: Survival after the local recurrence of rectal cancer is influenced by several factors. The aim of this study was to ascertain whether the time interval from primary surgery for rectal cancer to local recurrence diagnosis has any impact on survival.

Methods: Population-based data was collected from the Swedish Colorectal Cancer Registry. 7410 patients were operated with radical abdominal surgery for rectal cancer during the period 1995–2002. Of these, 386 (5%) developed a local recurrence as a first event. The patients were divided into two groups: early local recurrence (ELR), diagnosed <12 months after primary surgery, and late local recurrence (LLR), diagnosed ≥12 months after primary surgery. Kaplan–Meier curves and hazard ratios were calculated for survival analyses. Survival was calculated from the date of the local recurrence diagnosis to death or end of follow-up.

Results: Ninety-five patients had ELR and 291 patients LLR. Median time to local recurrence was 1.7 (0.1–7.9) years. Patients with a stage III primary tumour and non-irradiated patients were more common in the ELR compared with the LLR group. Factors that influenced survival were age at diagnosis of local recurrence ($p < 0.001$), stage of primary tumour ($p = 0.027$), and surgical resection of local recurrence ($p < 0.001$). Time to diagnosis of local recurrence had no influence on survival.

Conclusions: No difference in survival from date of diagnosis of local recurrence was seen between patients with ELR and patients with LLR. All patients with local recurrence should therefore be assessed for potential curative surgery, disregarding time to local recurrence.

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Keywords: Rectal cancer; Local recurrence; Time to local recurrence; Survival; Prognostic factors

Introduction

Locally recurrent rectal cancer is associated with high morbidity and mortality.^{1,2} The frequency of local recurrence used to be high, 20–40%, but after the introduction of total mesorectal excision (TME) as the preferred surgical technique and preoperative radiotherapy in selected cases with a high risk of local recurrence, the rate has dropped to 6–10% in population-based data.^{2,3} The majority of

local recurrences arise within two years after primary surgery, and more than 90% are diagnosed within five years.^{4,5} After the introduction of preoperative radiotherapy, a tendency of a delay in the appearance of local recurrences has been observed, and studies have reported a shorter survival after recurrence diagnosis in irradiated compared with non-irradiated patients.^{6–9} A more aggressive growth pattern in the primary tumour in irradiated patients has been suggested as one explanation for these results.⁸

The overall five-year survival in patients with a local recurrence is low, only 9%.^{2,10} With offensive multimodality treatment including extended surgery and preoperative radiotherapy, it can be improved to up to 40%.^{11,12} In

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15–20% of the patients with a local recurrence, distant metastases are found by the time of diagnosis, which minimizes their chances of curative intervention. Another 30% develop distant metastases despite radical surgery of the local recurrence.¹³

It has previously been reported that patients with early recurrent tumours have a poorer prognosis than those with late recurrences.^{14–17} However, only one of these reports has exclusively evaluated survival in patients with a local recurrence as a first event.¹⁷ Other studies have indicated no difference in survival between early and late local recurrences and the data remain ambiguous.^{18–21}

The aim of this population-based study was to investigate whether the time interval from primary surgery for rectal cancer to the diagnosis of a local recurrence has any impact on survival after the local recurrence diagnosis.

Materials and methods

National quality registry

Since 1995, all verified cases of rectal adenocarcinoma in Sweden are being reported to the Swedish Colorectal Cancer Registry. This is a national quality registry, to which information concerning patient- and tumour characteristics, type of surgery, presence and type of adjuvant treatment, postoperative morbidity and mortality data, incidence of local recurrence, distant metastases and death is reported by the responsible surgeon and oncologist. More than 32,000 patients with rectal cancer are included in the registry and coverage at the time of the study was above 97%.²² Validation of the registry has been made on several occasions, demonstrating a high quality of data when studying trends and patterns of rectal cancer, but an underreporting of complications.^{10,23,24} Each region's oncological centres are responsible for reporting to the national registry. Long-term follow-up data after primary surgery are reported after three and five years. Date of death is obtained from the Cause of Death Registry. Patients are identified by the unique personal identification number that all Swedish residents possess.

Study population

The inclusion criteria for the patients were: included in the Swedish Colorectal Cancer Registry, biopsy-proven adenocarcinoma of the rectum, tumour stage I–III, radically operated with abdominal surgery and with a local recurrence as a first event. The date of surgery for primary rectal cancer was limited to January 1st, 1995, to December 31st, 2002. Radical surgery was defined as radicality stated by both the surgeon and the pathologist. A local recurrence was defined as a tumour recurrence located in the lesser pelvis following radical surgery for rectal cancer. Patients with distant metastases diagnosed before, or simultaneously to, the local recurrence were excluded.

Time to local recurrence was defined as the time from radical surgery for primary rectal cancer to the diagnosis of the local recurrence. During the study period, all patients with rectal cancer were followed according to regional treatment programmes, as no national programme existed. Local recurrences were discovered after follow-up screening or by self-reported symptoms. Information regarding resection of local recurrences was received through the collection and review of medical journals.

The patient cohort was divided into two groups according to the time to local recurrence. A local recurrence less than 12 months after primary surgery was defined as an early local recurrence (ELR) and a local recurrence diagnosed 12 months or later after primary surgery was defined as a late local recurrence (LLR).

Ethical consent was obtained from the Regional Ethics Committee in Stockholm.

Statistical analysis

The distributional relationship between the dichotomized variable time to local recurrence and categorical variables was tested using the chi-square test of independence, and the chi-square test for trend was used for testing the relationship with ordinal variables. When analyzing time as a continuous variable, as in difference in time to local recurrence in irradiated and non-irradiated patients, we used the Mann–Whitney test.

In the survival analysis, survival time was calculated from date of diagnosis of the local recurrence to date of death or end of follow-up, which was set to April 30th, 2009.

Survival was estimated using the Kaplan–Meier method. The effect of clinical variables on time to death was studied using proportional hazards regression. Results from these models are presented as hazard ratios together with 95% confidence intervals. Reported p-values refer to Wald tests. A stepwise variable selection procedure using backward elimination was used to identify the strongest independent clinical variables. All factors were forced to be included in these models, but only factors with significant values ($p < 0.05$) were included in the final model. A bootstrap resampling procedure proposed by Sauerbrei et al. was used to assess the replication stability of the stepwise model.²⁵ This technique generates a number of samples (1000), each of the same size as the original data, by random sampling with replacement from the original dataset. The frequency of inclusion is indicative of the prognostic importance of the tested variable.

Results

In total, 9192 patients were abdominally operated for primary rectal cancer in Sweden between 1995 and 2002 (Fig. 1). From this number, 7410 (81%) were radically operated (R0) and 386 (5%) were diagnosed with a local

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