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ScienceDirect

EJSO 42 (2016) 801–807

EJSO the Journal of Cancer Surgery

www.ejso.com

Nodal involvement in luminal complete response after neoadjuvant treatment for rectal cancer☆

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Accepted 16 March 2016

Available online 28 March 2016

Abstract

Background: Pathological complete response (pCR) after neoadjuvant therapy in rectal cancer is correlated with improved survival. There is limited knowledge on the incidence of pCR at a national level with uniform guidelines. The aim of this prospective register-based study was to investigate the incidence and outcome of pCR in relation to neoadjuvant therapy in a national cohort.

Method: All patients abdominally operated for rectal cancer between 2007 and 2012 (n = 7885) were selected from The Swedish Colorectal Cancer Register. Twenty-six per cent (n = 2063) had neoadjuvant therapy with either long or short course radiotherapy with >4 weeks delay with the potential to achieve pCR. The primary endpoints were pCR and survival in relation to neoadjuvant therapy.

Results: Complete eradication of the luminal tumor, ypT0 was found in 161 patients (8%). In 83% of the ypT0 the regional lymph nodes were tumor negative (ypT0N0), 12% had 1–3 positive lymph nodes (ypT0N1) and 4% had more than three positive lymph nodes (ypT0N2). There was significantly greater survival with ypT0 compared to ypT+ (hazard ratio 0.38 (C.I 0.25–0.58)) and survival was significantly greater in patients with ypT0N0 compared to ypT0N1-2 (hazard ratio 0.36 (C.I 0.15–0.86)). In ypT0, cT3-4 tumors had the greater risk of node-positivity. The added use of chemotherapy resulted in 10% ypT0 compared to 5.1% in the group without chemotherapy ($p < 0.00004$).

Conclusion: Luminal pathological complete response occurred in 8%, 16% of them had tumor positive nodes. The survival benefit of luminal complete response is dependent upon nodal involvement status.

Keywords: Rectal cancer; Complete response; Lymph nodes; Neoadjuvant treatment

Introduction

Interest in non-operative management of rectal cancer has increased in recent years. Clinical complete response, cCR, is the absence of remaining tumor in the rectum after neoadjuvant treatment. In this situation, there is now a trend towards a "watchful waiting" strategy rather than radical surgery.[1–4] Single-center studies on selected patients with different treatment regimens describe a cCR incidence of 13–45% after chemoradiotherapy.[5–7] The lack of validated criteria to select patients for such non-operative management, however, makes it difficult to minimize the risk for recurrent disease.

Until now, most patients with rectal cancer have been treated with surgery with no regard to eventual cCR. Pathological complete response (pCR) means the absence of viable cancer cells in the surgical resection specimen (ypT0N0) after neoadjuvant treatment indicating excellent treatment response. Long-term preoperative radiotherapy (LRT), (e.g. 28 × 1.8 Gy), with 6–8 weeks interval to surgery can lead to sterilization of both tumor and adjacent lymph nodes and pCR rates of 10–15% can be achieved.[8–11] Short-term radiotherapy, 5 × 5 Gy (SRT)

☆ Some of the results were presented in a lecture at the Annual Meeting of the European Society of Colo-proctology in Barcelona 2014.

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http://dx.doi.org/10.1016/j.ejso.2016.03.013

0748-7983/

followed by immediate surgery, is usually used for less advanced tumors, but has no effect on down-staging due to the short time between radiation and surgery. Surgery can be postponed for several reasons thereby increasing the chance of SRT also having a down-staging effect. This is termed "SRT with delay". In a study on rectal cancer patients and SRT with unintended delay before surgery and without neoadjuvant chemotherapy, a group of 112 patients had a pCR rate of 8%.[12]

The use of added chemotherapy, usually 5-FU/capacitabine, has a well-documented effect on tumor down-staging with a two-to threefold increase in pCR achieved compared to RT alone.[8,11]

There is no clear correlation between the initial tumor stage and the outcome of neoadjuvant treatment, indicating that achievement of pCR is not limited to smaller tumors.[13]

Even if the primary tumor in the lumen disappears after neoadjuvant treatment (ypT0), there is still the risk of cancer cells in adjacent lymph nodes, a possible cause of tumor recurrence.

The majority of studies on pCR are based on small, single-centre experiences and little is known about the incidence and long-term outcome of pCR in a population-based cohort of patients. The present study describes the incidence and outcome of pCR after neoadjuvant treatment for advanced tumors and radical surgery in a national cohort of patients following uniform guidelines during a time period when non-operative management was not considered.

Methods

The Swedish Colo-Rectal Cancer Register (SCRCR) is a prospective population-based register collecting data from all colo-rectal cancer cases in Sweden.[14] This is a validated register with 99.5% immediate coverage and five-year follow-up data from 98% of patients.

Swedish guidelines[15]

Rectum constitutes the 15 most distal centimeters of colon and is divided in to three 5 cm long sections. Neoadjuvant standard long course therapy is given for T4 rectal cancer, and tumors with suspected involvement of lateral lymph nodes or an involved circumferential resection margin (CRM).

Standard chemoradiotherapy (CRT) treatment includes LRT + concomitant 5-FU/capacitabine followed by surgery after a delay of 6–8 weeks. Chemotherapy is omitted in weak patients.

The standard treatment for T3b tumors in the middle and lower rectum as well as meso-rectal N+ tumors is SRT, provided the CRM is clear. Surgery is usually performed within five days of completion of RT. T1-2 and T3a tumors in the lower rectum and T3b tumors in the upper rectum are operated on without prior neoadjuvant therapy.

Decisions on neoadjuvant therapy, surgery and adjuvant therapy are usually made at a multidisciplinary team conference, and are based on national guidelines and knowledge of the individual patient.

During the study period the Stockholm-III Trial was ongoing, in which patients were randomized to immediate surgery or surgery 6–8 weeks after SRT in cT1–cT3 tumors.[10] Patients from the Stockholm-III trial made up less than 2% of the study population in the present study.

Patient identity and data were traceable through access to the SCRCR after approval for this study from the Regional Ethics Committee.

The board of the SCRCR also approved the study.

Patients

Patients registered in the SCRCR between 2007 and 2012 were included in the study. Since 2007 the register has collected data on MRI staging, hence the starting point for this study. The study cohort consisted of 11,226 patients with a median age of 71 years, fifty-nine per cent were males. An abdominal operation was performed on 7885 patients. Twenty-six per cent (2063 patients) were classified as having potential for pCR after receiving LRT or SRT with delay, with or without chemotherapy, before abdominal surgery. This group was labeled "potential complete responders" and formed the basis of this study (Table 1). From that group the patients with ypT0 were identified.

According to Swedish guidelines for neoadjuvant treatment, the majority of that group had advanced cT3 (48%) and cT4 (36%) cancer, and 56% had chemotherapy as well as RT.

Table 1
Description of the study population.

			Female	M1[a]
Rectal cancer (2007–2012)	n – %	11,226	41%	20%
	age (median)	71	71	
Abdominally operated[b]	n – %	7885	40%	8%
	age (median)	69	69	
Anterior resection	n – %	3940	42%	12%
	age (median)	67	66	
Abdomino-perineal resection	n – %	2837	38%	11%
	age (median)	70	70	
Hartmann's procedure	n – %	1108	42%	8%
	age (median)	78	77	
Potential complete responders (Long-term RT or short-term RT with delay, +/– chemotherapy.)	n – %	2063	40%	13%
	age (median)	66	67	
Long-term radiation	n – %	1179	41%	10%
	age (median)	64	64	
Short-term radiation with delay	n – %	884	38%	16%
	age (median)	71	73	

[a] Ten of the ypTO patients had distant metastases (M1).
[b] 368 Patients with rectal cancer had a local excision of the tumor and were not included in cohort.