Local recurrence in rectal cancer : mechanisms of development, patterns of relapse and treatment options

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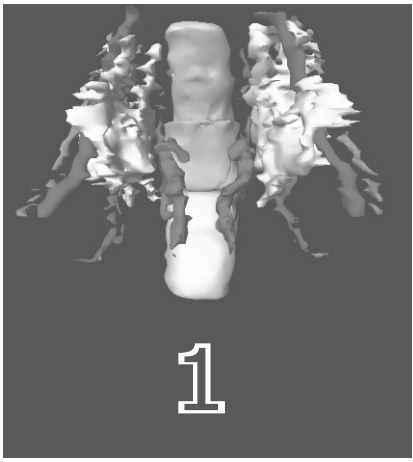
Chapter



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General introduction

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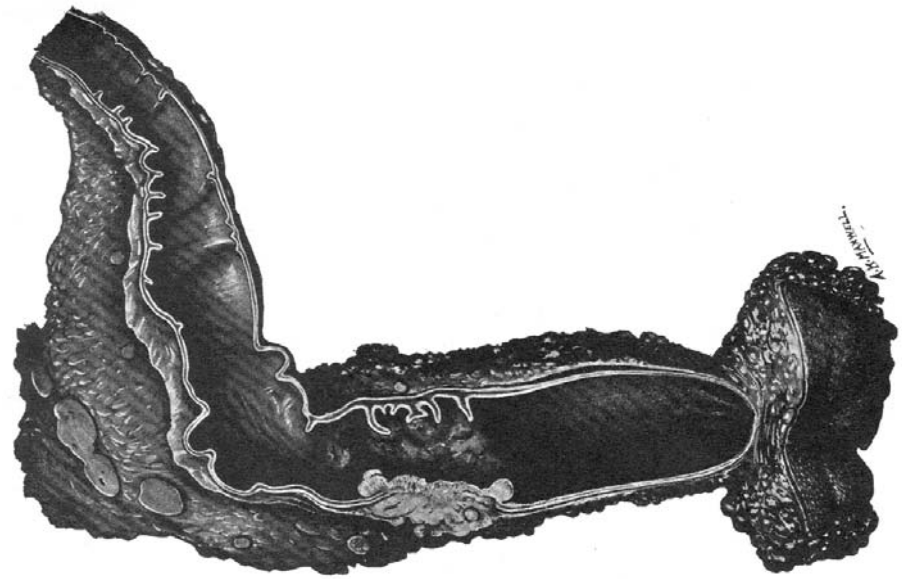
In the Netherlands around 10.000 patients are diagnosed with colorectal carcinoma every year (www.oncoline.nl), of who about 2500 have rectal carcinoma (Figure 1.1). It is the third most common cancer in men (after prostate and lung cancer) and the second most common in women (after breast cancer). It is expected that in 2015 the incidence of colorectal carcinoma will be around 14.000.
In the treatment of rectal cancer a multi-disciplinary approach is the best way to achieve optimal outcomes. Imaging, (neo)adjuvant therapy, surgery and pathology all have a specific role in the treatment of rectal cancer.

Figure 1.1



Source figure 1.1:
Ernest Miles. Cancer of the rectum. Transactions of the medical society of London, vol xlvii. London, Harrison and Sons, 1926

Imaging

Endorectal ultrasound (EUS) is the most accurate imaging modality for the evaluation of early rectal tumors[1;2]. Computed tomography (CT) imaging performs well in staging of advanced disease[3], but resolution is low, making detailed evaluation of structures difficult. Since the introduction of magnetic resonance imaging (MRI) major progress has been achieved in the preoperative evaluation of local tumor extent. MRI has proven to be very accurate in the visualisation of the relation of the tumor with the mesorectal fascia[4;5].

However, although the extent of the primary tumor can be assessed well, reliable detection of nodal metastases is not yet possible. CT is unreliable for the assessment of lymph nodes, because only the lymph node size can be evaluated [6;7]. Micro-metastases

are missed, as well as small metastases in non-enlarged lymph nodes. MRI is reported to be superior to CT, because it can rely on additional morphological criteria of lymph nodes, such as signal intensity and border contour[5;8;9].

In preoperative staging the definition of locally advanced disease is a point of discussion. Some authors define it as any T3 or T4 tumor[10;11], some as a threatened or involved mesorectal fascia (T3+ or T4 tumors)[12], while others also include lymph node positive disease[13;14].

(Neo)adjuvant treatment

In Western countries neoadjuvant treatment has become standard in the treatment of rectal cancer. A short course of preoperative radiotherapy (5x5 Gy, followed by surgery within 5 days) has shown to reduce local recurrence rates significantly[15;16] and is more effective than postoperative radiotherapy[17]. In a Swedish trial[16] preoperative radiotherapy even improved survival, but this was not shown in the Dutch TME trial[15], with the difference that in the total mesorectal excision (TME) trial surgery was standardized.

In locally advanced disease a short course of preoperative radiotherapy is not sufficient, since it can not downstage the tumor to facilitate a radical surgical resection. In these tumors rather a long course of radiotherapy (45 - 50 Gy in fractions of 1.8 - 2.0 Gy) combined with chemotherapy is the neoadjuvant treatment of choice[18].

The role of adjuvant chemotherapy following preoperative (chemo)radiotherapy is a subject of debate and research in several European countries. It is known that adherence to adjuvant chemotherapy is generally poor. Gradually evidence is increasing that chemotherapy can possibly improve overall survival[19-21] and local recurrence rates[10], at least in selected groups of rectal cancer patients.

Surgery

Surgery is the principal treatment for cure. The main purpose of surgical treatment is en bloc excision of the primary tumor with its locoregional lymph nodes. Furthermore, the focus of surgery is on a radical resection not only at the distal margin, but even more important at the circumferential margin. With the total mesorectal excision (TME) technique, introduced by Bill Heald[22], the rectum is removed along the 'holy plane', an avascular interface between the mesorectal fascia and the parietal dorsolateral pelvic fascia. If the rectum is not removed within it's envelope of mesorectal fascia, a non-radical resection with persistence of tumor cells and subsequent high chance for local recurrence is likely to occur[23].

With the total mesorectal excision procedure local recurrence rates and survival have improved[24;25]. However, the results of the TME technique for low tumors operated by abdominoperineal resection (APR) are not as good as for midrectal or higher tumors operated by means of a low anterior resection (LAR), with still a considerable local recurrence rate[26;27]. This is ascribed to the difficulty to obtain a wide circumferential margin and the higher rate of perforations of the mesorectum and bowel wall, especially in the case of abdominoperineal resection[26;28;29]. In the TME trial, abdominoperineal resection was associated with higher circumferential resection margin involvement[30].

In Western countries, total mesorectal excision has become the standard, often

combined with neoadjuvant treatment. In Eastern countries however, initiated by surgeons in Japan, the lateral lymph node dissection (LLND) has become the gold standard in cases of advanced rectal cancer[14;31], without the use of (neo)adjuvant treatment regimens. In this technique, all lymph nodes along the internal and external iliac and obturator arteries are resected, with similar oncologic outcomes as in Western series[32;33].

Intra-operative radiotherapy

Preoperative radiotherapy has been used to facilitate surgical resection by downsizing locally advanced rectal carcinoma. Still, in many patients areas at risk will remain, but normal tissue tolerance limits the dose of radiotherapy[34]. An approach to overcome dose limitations is to apply a intra-operative radiotherapy (IORT) boost to a specific area[35]. IORT allows the deliverance of a boost, biologically comparable to an additional 30 to 40 Gy fractionated irradiation, to a well-defined volume under direct vision, with a possibility to shield or remove dose-sensitive structures. However, the IORT equipment is expensive and the logistics are complex. Therefore in Europe only a few institutes use this type of combination therapy[35-38]. The treatment results of these institutes are favourable, but there are no reports in which the additional value of IORT has been quantified.

Pathology

The Tumor, Node, Metastasis (TNM) system (Table 1.1) of the international union against cancer (IUCC) defines the stage of rectal cancer[39]. Furthermore, the type and grade of the tumor are of prognostic value in the pathological assessment. In the last decades the importance of pathologic quality control of the surgical specimen has become essential in the multi-disciplinary approach of rectal carcinoma[30]. The method of Quirke[23], in which the tumor and mesorectum are sliced in the transverse plane, evaluates the completeness of the mesorectum and the tumor distance from the lateral margins. A direct inverse relation between tumor or lymph node distance to the mesorectal fascia and

Table 1.1 TNM staging system

	TNM		Stadium
Tis	N0	M0	0
T1-2	N0	M0	I
T3	N0	M0	II
T4	N0	M0	
T1-2	N+	M0	III
T3	N+	M0	
T4	N+	M0	
Tx	Nx	M1	IV

Tis; involves only mucosa, T1-2; extension into submucosa or muscularis propia,
T3; growth through muscularis propria into submucosa,
T4; growth through wall of rectum into nearby organs
N0; no lymph node involvement, N+; lymph node involvement,
M0; no distant metastases, M1; distant metastases

local recurrence has been established; a distance of 1 mm or less is associated with a high local recurrence rate and in some studies even with a lower survival rate[30;40]. Since the introduction of neoadjuvant therapy pathologic staging has become more difficult, due to fragmentation of the tumor and remaining tumor deposits[12].

Local recurrence

Local recurrence is defined as any rectal cancer recurrence in the small pelvis. It is associated with serious morbidity and shortened life expectancy[41]. Since the introduction of total mesorectal excision combined with neoadjuvant (chemo)radiotherapy, locally recurrent rectal cancer has become less common. Whereas primary rectal cancer treatment is gradually standardizing, based on preoperative evaluation of the tumor extent, local recurrence treatment is still controversial. However, the general idea has shifted from non-intervention or palliative (chemo)radiotherapy to more aggressive multimodal approaches combined with intended radical surgery.

Recent studies have described that radicality of the resection of the local recurrence is the most significant predictor of improved survival[42-44]. Since these extensive treatment strategies can cause serious morbidity, selection of potentially resectable tumors thus has to receive major emphasis in the preoperative work-up. If with imaging techniques the exact location and invasion patterns can be determined, local recurrence treatment can also become more tailored.

Outline of the thesis

The central theme of this thesis is the patterns of local recurrence of rectal cancer. By determination of the location of locally recurrent rectal cancer on imaging and relating these to patient, treatment and tumor variables, the mechanism of local relapse genesis is reconstructed. By doing this the effect of neoadjuvant treatment, surgery, intra-operative radiotherapy and adjuvant treatment on local control can be quantified.

First, patterns of local recurrence are described for rectal cancer in general (Chapters 3-5) and then only for locally advanced rectal cancer (Chapters 6-7). Subsequently, the effect of preoperative evaluation of local recurrent rectal cancer on results of the multimodality treatment of local relapse is analyzed (Chapters 8-9).

In the second chapter the history, operation techniques and nerve-sparing procedures of rectal cancer surgery are discussed and the differences between East and West are clarified.

The third chapter investigates the patterns of local recurrence in the TME trial, a large multicenter randomized study analyzing the effect of preoperative radiotherapy in total mesorectal excision surgery. The effect of preoperative radiotherapy on local recurrence is analyzed and possible flaws in the surgical sphincter-saving and non-sphincter-saving techniques are investigated.

The fourth chapter analyzes a cohort of patients operated at the National Cancer Center Hospital in Tokyo. The purpose is to discuss the effect of the lateral lymph node dissection on patterns of local recurrence, in order to understand the role of lateral tumor particles in local recurrence genesis.

Subsequently, in the fifth chapter, patients from the TME trial are compared to a similar group of Japanese patients. The effect of the more extended Japanese surgery and of preoperative radiotherapy on extra-mesorectal tumor particles is studied.

In the sixth chapter the effect of multimodality treatment of locally advanced disease on patterns of local recurrence are studied in patients operated in the Catharina Hospital in Eindhoven. Focus is on the effect of intra-operative radiotherapy and the risk factors for local recurrence.

In the seventh chapter the patients from four European treatment centers for non-metastasized locally advanced rectal carcinoma are pooled. The basic treatment principles; preoperative (chemo)radiotherapy, surgery, and intra-operative radiotherapy. Also the effect of adjuvant chemotherapy is analyzed.

The eighth chapter focuses on the radiological evaluation of locally recurrent rectal carcinoma in patients of the Catharina Hospital. The role of magnetic resonance imaging on the prediction of localization and extent of growth is investigated.

In the ninth chapter the results of intra-operative radiotherapy containing multimodality treatment for locally recurrent rectal cancer in the Catharina Hospital are evaluated. The oncologic results, in terms of radicality, local re-recurrence, metastasis rate and cancer-specific survival, are related to the subsite of local recurrence.

Finally, in the tenth chapter, the previous chapters are summarized, a general discussion is included and future perspectives are contemplated.

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