Lateral lymph nodes in rectal cancer

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Chapter 1

General introduction & thesis outline

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Colorectal cancer affects annually roughly 13,000 people in the Netherlands, of which roughly one-third are located in the rectum, the final portion of the large intestines[1]. This makes colorectal cancer the fifth most frequent type of cancer[2]. The incidence of colorectal cancer has increased slightly since the national screening program was introduced in the Netherlands in 2014, and subsequently decreased. Rectal cancer occurs more frequently in men (approximately 60%) and predominantly in patients ≥60 years of age[1]. The aetiology is multifactorial, with risk factors such as nutrition and lifestyle, genetic components, and underlying intestinal (inflammatory) disease[1]. The most common symptoms associated with the initial presentation of rectal cancer are blood loss and changes in stool patterns.

Staging

The primary modality for the examination of a rectal tumour and regional lymph nodes is magnetic resonance imaging (MRI). Distant metastases and non-regional lymph nodes are assessed using computerized tomography (CT). For regional mesorectal lymph nodes, the number of nodes, their size, and the presence or absence of additional malignant features (heterogeneity, irregular border, round shape) are taken into account. Limited sensitivity and specificity have been shown for predicting malignancy when only considering size of mesorectal lymph nodes on MRI (55-78%)[3, 4]. However, when size is combined with the presence or absence of malignant features, the sensitivity and specificity increases to 85-95%[4].

Clinical staging of rectal cancer is based on imaging of the primary tumour (T-stage), regional lymph nodes (N-stage) and whether or not metastases are present in distant organs or non-regional lymph nodes (M-stage) (TNM classification)[5, 6]. Stage I rectal tumours are limited to the inner layer of the rectum and have no metastases in either regional lymph nodes, or distant organs/non-regional lymph nodes (T1-2,N0,M0). In stage II tumours, the primary tumour has spread through the muscular layer of the rectum, but again, there are no regional or distant metastases (T3,N0,M0). Stage III represents any growth of the primary tumour with spread to regional lymph nodes outside the rectum, but no metastases in distant lymph nodes or organs (T(any),N1-2,M0), while in stage IV, distant metastases are present (T(any),N(any),M1)[5, 6].

Table 1. based on the TNM classification of UICC, 8th edition 2016[7]

TNM classification		Description
T-stage	T0	No evident primary tumour
	T1	Tumour invades the submucosa
	T2	Tumour invades the muscularis propria
	T3	Tumour invades the subserosa
	T4	Tumour invades other organs (a: through visceral peritoneum, b: into other structures)
N-stage	N0	No metastases in regional (mesorectal) lymph nodes
	N1	Metastases in 1-3 regional (mesorectal) lymph nodes
	N2	Metastases in 4+ regional (mesorectal) lymph nodes
M-stage	M0	No distant metastases
	M1	Distant metastases into organs and/or non-regional lymph nodes

The largest proportion of patients (37%) initially present with stage III rectal cancer[1]. The average five-year overall survival (OS) rate for patients with rectal cancer is 67%, but decreases rapidly with increasing stage; the five-year OS rate is 94% for patients who present with stage I, 82% for stage II, 75% for stage III and 14% for stage IV[1].

Treatment of (locally advanced) rectal cancer

The staging of rectal cancer is important for subsequent treatment decisions[3]. According to current Dutch guidelines, patients with stage I rectal cancer are treated with surgery, without neoadjuvant treatment[5]. Surgical options for stage I rectal tumours differ depending on the size and invasion depth of the tumour. Patients with T1 tumours can be treated via organ preservation techniques such as transanal minimally invasive surgery (TAMIS), while patients with T2 tumours typically undergo total mesorectal excision (TME) surgery. In cases of low-risk stage II (for example; cT3a-b,MRF-,N0M0), again, only rectal surgery without neoadjuvant treatment is the preferred treatment. In this manner, patients with less invasive tumours can be spared from the potential side-effects of neoadjuvant irradiation.

Neoadjuvant treatment is aimed at achieving sufficient downsizing and downstaging so that radical surgery is possible, thereby facilitating better local control rates[8]. During the last decade, neoadjuvant therapy has also been used to enable organ preservation, to avoid a permanent stoma, and thus improve quality of life. Current neoadjuvant radiotherapy in the Netherlands knows two main forms: short-course radiotherapy (25Gy in 5 fractions [5x5Gy; SCRT]) or chemoradiotherapy (45-50Gy in 25-28 fractions of 1.8-2Gy, with oral capecitabine 825mg/m^2 b.i.d. to increase the tumours sensitivity to radiotherapy [CRT]). For patients with high-risk stage II rectal cancer (for example; cT1-3c-d,MRF-,N0M0) or primarily resectable stage III rectal cancer (cT1-3,MRF-,N1M0), neoadjuvant radiotherapy can be considered. Neoadjuvant radiotherapy is indicated for patients with locally advanced rectal cancer, without distant metastases, that require downsizing prior to surgery (cT4 and/or MRF+), as well as for those with high-risk features for local recurrence. Factors for increased risk of local recurrence are a cN2-stage, the presence

of extramural venous invasion (mrEMVI: in which the tumour encroaches on local blood vessels) or visible lateral lymph nodes (LLNs: explained in the next section).

Neoadjuvant CRT has long been standard of care for downsizing, but SCRT with long interval until surgery, or followed by consolidation chemotherapy (RAPIDO schedule), have become alternative schedules in the Netherlands. The latter schedule is also referred to as total neoadjuvant treatment (TNT). CRT preceded or followed by systemic chemotherapy are also increasingly used in TNT schedules for locally advanced rectal cancer worldwide with promising results[9-12].

If there is a clinical complete response on the restaging MRI after neoadjuvant (C)RT or TNT schedule, a 'watch & wait' approach with long-term intensive surveillance can be chosen after shared decision making[13-15]. However, in almost all other cases, radical surgery remains the primary treatment modality. Surgery is based on the principle of total mesorectal excision (TME), in which the rectum and all surrounding mesorectum (within an intact MRF) are removed following anatomical borders, to ensure that all potentially malignant tissue has been removed[16, 17]. In cases of very low primary tumours with an inability to ensure a negative distal margin, involvement of the (external) sphincter, or invasion of the levator ani muscle, patients may undergo an abdominoperineal resection (APR) with an end colostomy. In very advanced cases, where the tumour has spread outside the rectum and into other structures or organs, such as the vagina, prostate, seminal vesicles, bladder or uterus, a 'beyond TME' approach or pelvic exenteration, is indicated.

In contrast to colon cancer, the advantages of adjuvant chemotherapy for rectal cancer are debated[18]. A number of studies over the last few decades have failed to establish a statistically significant benefit in survival for postoperative adjuvant chemotherapy after neoadjuvant therapy in rectal cancer patients[19]. Furthermore, there are concerns regarding compliance rates. Results from three studies found a mean compliance rate of 49% with a range from 32%-73%[20-22]. Such limited compliance would majorly affect efficacy. Accordingly, current treatment schedules are focussed on neoadjuvant therapy.

Lateral lymph nodes

The presence of (enlarged) LLNs, especially in patients with low rectal cancer, has been linked to an increased risk of local recurrence[23, 24], though their aetiology is unclear. LLNs are located outside the mesorectum in the lateral compartments of the pelvis, near the internal iliac and obturator vessels. Anatomical studies have demonstrated that lymphatic pathways appear to follow the arterial routes of the rectum, in which drainage of the internal iliac and obturator compartments follow the middle rectal artery [25-27].

The primary size has been suggested to be particularly important in the determination of LLN malignancy. The international Lateral Node Consortium study of 1,216 patients found that LLNs measuring at least 7mm (short-axis) resulted in a five-year lateral local recurrence rate of 19.5%[24, 28], compared to standard local recurrence rates for rectal cancer which are around 5-10%[27, 29]. The presence of (enlarged) LLNs appeared therefore to hamper local control. Other studies adhered to other size thresholds when defining 'enlarged' LLNs (such as ≥8mm[30] or ≥10mm[31]).

There is also limited (inter)national consensus regarding the appropriate treatment of malignant LLNs. Eastern cultures, primarily in Japan, have traditionally opted for total mesorectal excision (TME) surgery and a lateral lymph node dissection (LLND) in all patients with low, locally advanced rectal cancer (described in more detail in chapters 2 & 3). During a LLND, all lymphatic tissue from the lateral (internal iliac and obturator) compartments is surgically removed. Japanese trials have demonstrated good long-term local control rates after TME and prophylactic LLND[32-36], while Western physicians have primarily relied on neoadjuvant therapies and TME surgery to treat patients with LLNs. For example, one comparative study found similar five-year local recurrence rates for a Japanese cohort who underwent TME+LLND without neoadjuvant treatment (6.9%) compared to a Dutch cohort receiving radiotherapy and TME surgery, without LLND (5.8%) [37]. One major factor explaining these differing approaches is the limited exposure and experience of Western surgeons with the LLND procedure. Evading the LLND means that morbidity associated with the LLND procedure, such as bleeding or nerve damage, which is believed to occur more often in the more obese Western patient, can be avoided[23, 25].

Another point is that many Western physicians believe lateral nodal disease to represent metastatic, not locoregional, disease[38]. However, results from the Lateral Node Consortium study do not support this and found that the presence of enlarged LLNs only influenced local recurrences rates, not overall survival or distant metastasis rates[24, 28]. Accordingly, recent years have witnessed a paradigm shift during which Western physicians have started considering lateral nodal disease to represent local disease, with possible advantages for additional surgery aimed at enlarged LLNs. These procedures range from individual 'node-picking' or incomplete LLNDs, to full LLND following anatomical landmarks. Results from very small cohorts[24, 39] have led to uncertain conclusions.

Aim of this thesis

There is a lack of knowledge regarding the definition, classification, and appropriate treatment of malignant LLNs in patients with locally advanced rectal cancer. The primary aim of this thesis is to increase the knowledge regarding LLNs and improve treatment practices for patients with rectal cancer and lateral nodal disease.

Thesis outline

This thesis is divided into three parts. Part I focuses on the historical and cultural variation present between Eastern, predominantly Japanese, and Western clinicians with regard to lateral nodal disease and discusses the different concepts regarding the appropriate treatment of LLNs (chapters 2 & 3). Results in chapter 4 demonstrate that variation exists between radiologists, radiation oncologists and surgeons concerning their terminology and treatment guidelines for LLNs and the lateral compartments.

Part II focusses on the awareness and knowledge of radiologists regarding LLNs. The primary and restaging MRI reports of 202 patients with rectal cancer from one tertiary centre over a span of eight years are examined to see how often LLNs are mentioned (chapter 5). Prior to participation in the Snapshot Rectal Cancer 2016 study, local radiologists from each centre in the Netherlands participated in a dedicated training session. Whether inter-physician variation is present between 53 consultant abdominal radiologist for determining short-axis size and anatomical location of LLNs is explored and compared to results after training (chapter 6). The classification and description of LLNs in original MRI reports for 1,096 patients in 2016 are then compared to present-day results after re-review of the images and training (chapter 7).

Part III addresses a number of fundamental prognostic questions regarding LLNs with data from the Snapshot Rectal Cancer 2016 study. Which LLN features are predictive for increased (lateral) locoregional recurrence rates (chapter 8), and the coverage of these LLNs with routine (chemo)radiotherapy (chapter 9). Furthermore, whether patients with enlarged LLNs who underwent additional LLN surgery in 2016 resulted in different oncological outcomes compared to patients with enlarged LLNs who did not undergo additional surgery, is explored in chapter 10.

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