Magnetic Resonance Imaging or Contrast-Enhanced Computed Tomography of the Liver as Standard Workup Before Treatment for Rectal Cancer

Degree Project in Medicine

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Gothenburg, Sweden 2018

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ABSTRACT

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Introduction: The liver is the most commonly affected site regarding rectal cancer metastasis. The Swedish national cancer care guidelines recommend a routine of a preoperative contrast-enhanced computed tomography (CT) to examine the liver for metastases before rectal cancer treatment. The NU Hospital Group (NU) conforms to the national guidelines. The Sahlgrenska University Hospital (SU) differs by conducting magnetic resonance imaging (MRI) of the liver.

Objective: To compare the efficiency of MRI with contrast-enhanced CT as the index examination of the liver in patients with newly diagnosed rectal cancer.

Methods: Clinical data regarding 320 patients with rectal cancer (160 from SU and 160 from NU) were collected from the Regional ColoRectal Cancer Register, 2013–2015. Information regarding such as liver examinations and surgery was collected from hospital records. All index liver examinations that did not confirm or rule out liver metastasis were considered “inconclusive” and subsequently re-evaluated by two radiologists.

Results: 274 patients were analyzed. 13 % in the MRI group and 15 % in the CT group underwent supplementary liver examinations before treatment for rectal cancer ($p = 0.635$). Within 18 months after the index examination, a total of 17 % of patients were diagnosed with liver metastases in both groups combined ($p = 0.765$), and 8 % of patients in the MRI group versus 2 % in the CT group were treated with liver surgery ($p = 0.016$).

Conclusions: MRI did not show any clinical advantage over contrast-enhanced CT as the index examination of the liver among patients with newly diagnosed rectal cancer. Thus, this study gives no reason to change the current Swedish national guidelines for rectal cancer.

Key words: Magnetic resonance imaging, computed tomography, rectal cancer, liver metastasis

INTRODUCTION

Between 2005 and 2015, there was a 33 percent rise in the number of patients who were diagnosed with cancer worldwide. A large proportion of this increase in incidence was due to population growth and ageing, and the incidence is expected to rise further (1). During the same period, there was also a 17 percent worldwide increase in the total number of cancer-related deaths (2). In 2015, 16 percent of all deaths were caused by cancer, which made it the second leading cause of death globally after cardiovascular disease (2).

In the view of the increased incidence, every step of cancer diagnosis and treatment should be evaluated regarding its outcomes. Therefore, this study is aimed to evaluate a part of the radiological workup before treatment for rectal cancer.

Rectal Cancer

Rectal cancer implies cancerous tumors in the most distal 15 cm of the large intestines (the rectum) and is often defined in combination with colon cancer as colorectal cancer.

Epidemiology

In 2015, colorectal cancer was the third most common type of cancer worldwide in both sexes combined, after breast cancer and tracheal/bronchus/lung cancer (1). According to the 2011 statistics from the Swedish National Board of Health and Welfare, rectal cancer accounted for approximately one-third of all cases of colorectal cancer and was by itself the ninth most common type of cancer in Sweden (3). In 2011, the Swedish rectal cancer incidences among men and women were 24.6 and 17.3 cases per 100 000 persons respectively, affecting nearly 2 000 individuals. The same year, the total number of Swedish individuals with rectal cancer (the prevalence) was 15 846 (3). On average, only five percent of patients are diagnosed before 50 years of age, which makes rectal cancer a rarer disease in younger populations (4).

Risk factors

The average lifetime risk of getting colorectal cancer in western populations range 3–5 percent (5), and there are several risk factors to consider. According to a report from the American Institute for Cancer Research, men are at higher risk of getting colorectal cancer than women (6). The report further states that increased body weight, consumption of red or processed meat, prolonged heavy smoking, and alcohol intake correlate to increased risks of colorectal cancer (6). On the other hand, intake of vitamin D and calcium could decrease the risk, as could the consumption of milk, possibly also yoghurt, and other foods such as whole grains, poultry, and fish (6, 7).

Though the majority of colorectal cancers appear sporadically, some are genetically conditioned. About 15–20 percent of patients with colorectal cancer have colorectal cancers in their family histories, and another 5–10 percent even suffer from hereditary colorectal cancer syndromes (5). Having a first-degree relative diagnosed with colorectal cancer at 50–70 years of age nearly doubles the average lifetime risk of being diagnosed with colorectal cancer. Having an even younger first-degree relative with colorectal cancer nearly triples the risk (5).

Finally, apart from environmental factors and hereditary conditions, other diseases could also affect the risk of getting colorectal cancer. Both type 2 diabetes mellitus and inflammatory bowel diseases, particularly prolonged and widespread ulcerative colitis, seem to increase the risk of developing colorectal cancer (5).

Pathophysiology

All factors that increase the risk of colorectal cancer do so by affecting the cells and tissues of the large intestines in one way or another. Over the years, gene mutations and epigenetic alterations will accumulate in colorectal epithelial cells. As a result, cytological abnormalities or neoplasms, such as adenomas, can begin to form (5). It is widely accepted that colorectal cancer typically emerges from an early adenoma that evolves into a more advanced adenoma before finally becoming a malignant tumor. However, the proportion of adenomas that turn malignant and the time this transition takes are difficult to study and still subjects of discussion. In a follow-up study of polyps ≥ 1.0 cm in diameter, the cumulative risk of malignancy at the site of the index polyp after 5, 10, and 20 years was 2.5 percent, 8 percent, and 24 percent respectively (8).

Diagnosis and the Swedish national cancer care guidelines for rectal cancer

Rectal bleeding, more frequent defecation, diarrhea, incomplete evacuation of stool , mucous in stool, form changes in stools, constipation, and pain are potential symptoms of rectal cancer (4, 9). A combination of these symptoms provides high predictive values for rectal cancer and should lead to further clinical assessments (4).

The current Swedish national cancer care guidelines for rectal cancer were implemented in 2016 to limit the differences in how patients with a suspected or confirmed rectal cancer are treated between regions and hospitals in Sweden (4). According to these guidelines, presenting at least one of the following symptoms should result in an immediate referral for a colonoscopy: changes in otherwise stable bowel habits for >4 weeks without any apparent explanation in patients older than 40 years of age, clinical imaging findings indicating rectal cancer, rectal palpation or endoscopy findings indicating rectal cancer, visual blood in stools in high-risk patients, visual blood in stools, even though rectal palpation or endoscopy is unable to locate an apparent bleeding source, and/or anemia that cannot be explained by standard anemia assessments. If the colonoscopy is inconclusive, a computed tomographic colonography may provide additional information for a more accurate diagnosis (4).

After confirming the presence of rectal cancer, the current Swedish national guidelines recommend a routine preoperative radiological examination of the pelvic region using magnetic resonance imaging and of the thorax/abdomen using contrast-enhanced computed tomography for prognosis estimations and an accurate clinical cancer staging (4). The staging conforms to the Union for International Cancer Control (UICC) *TNM Classification of Malignant Tumors* (T – the extent of invasion and size of the primary tumor, N – the absence or presence of regional lymph node metastases, M – the absence or presence of distant metastases; the addition of numbers to these three components indicates the extent of the malignant disease). The TNM classification can be further translated into stages I–IV, where IV accounts for the most advanced cancer stages (10).

Treatment

With all the necessary diagnostic information at hand, colorectal surgeons (if needed, also liver and/or thoracic surgeons), oncologists, radiologists, pathologists, and contact nurses, gather in multidisciplinary team conferences (MDT) to discuss and, if no additional examinations are needed, subsequently make decisions regarding the best possible treatments for each patient. Over the past years, these conferences have become very important for the multimodal management and treatment of patients with rectal cancer (and other types of cancer) (4). Treatment initiations should follow as soon as possible after treatment decisions are made. As a matter of fact, according to the current Swedish national guidelines, the time between the date of rectal cancer diagnosis and treatment initiation should not exceed 42 days (4).

The standard treatment for rectal cancer is resection surgery (4). Some patients, depending on their cancer stage, will receive neoadjuvant (preoperative) radio- or radiochemotherapy to down-stage the cancer before surgery. Doing so may limit the risks for persistent micrometastases (microscopic lesions spatially separated from the gross tumor) and local recurrences at the site of the index tumor after excision, thus improving the long-term outcome (4).

For rectal cancers that are staged according to the TNM classification as T1, T2, T3, and sometimes even T4 after neoadjuvant radio- or radiochemotherapy, a total mesorectal excision is currently the standard surgical technique (5). It is performed by excising the rectum while concurrently and in one piece completely removing the rectal mesentery, including all local mesenteric lymph nodes (5).

There are currently three different rectal excision procedures to consider for radical resection of the primary rectal tumor. Firstly, there is anterior resection, meaning that the rectum is removed, and an anastomosis is formed. At the same time, a loop-ileostomy is often formed to temporarily protect the anastomosis during the initial period after surgery (4). The “covering ileostomy” can be expected to reduce the clinical consequences if anastomotic dehiscence would occur (11). A recent study reported that an early closure of the ileostomy could further reduce the risk for complications (12). Secondly, if sphincter preservation is not possible, an abdominoperineal excision is currently the preferred procedure. It involves removal of the anus and sometimes also parts of the pelvic floor. Because the anus is removed, a permanent colostomy is created (4). Finally, there is Hartmann's procedure, which is recommended for patients with sphincter dysfunction and/or high morbidity. This procedure is largely equivalent to the anterior resection but differs by resulting in a permanent colostomy rather than an anastomosis (4). In carefully selected cases, most often among fragile and elderly patients, local excision of the rectal tumor, such as a transendoscopic excision, can be used as an alternative to resection surgery (4).

If a patient presents urgent symptoms that are caused by an obstructive rectal tumor, emergency surgery may be performed to relieve the obstruction. One method is forming a defunctioning stoma without resection of the primary tumor (4). As an alternative in selected patients with a more proximal rectal cancer, colonic stenting could be used to avoid emergency surgery (13, 14). A stent or defunctioning stoma can also be used as symptom relief in palliative settings (4).

Prognosis

According to the Swedish National Board of Health and Welfare, the prognosis for rectal cancer has improved over the last decades due to enhanced diagnostic methods and oncological treatments (3). The Swedish overall 10-year relative survival has increased by approximately 20 percent since the 1980s. In 2011, the overall relative 5-year/10-year survival rates after rectal cancer among Swedish men and women were 62.9/53.9 percent and 64.2/58.0 percent respectively (3).

Although the overall survival has improved, rectal cancer treatments are still frequently associated with serious complications, such as anastomotic leakage, toxicity after chemotherapy, pelvic floor dysfunction, fecal incontinence, erectile dysfunction, and dyspareunia (5). Moreover, spreading of rectal cancer (metastasis) to other locations in the body can cause additional symptoms and require other treatments that also could affect the prognosis and the quality of life (5). Therefore, information regarding possible metastasis is important to acquire at an early stage of the disease before treatment decisions are made at multidisciplinary team conferences (4).

Rectal Cancer Liver Metastasis

The liver is the most commonly affected site regarding rectal cancer metastasis (15). Although there is currently no actual consensus on how to exactly categorize rectal cancer metastasis with respect to when in time it is diagnosed, metastasis that is detected within six months after the rectal cancer diagnosis could be defined as synchronous. Metastasis that is detected at a later stage could be defined as metachronous (15). Approximately 14–20 percent of all patients with rectal cancer are diagnosed with synchronous liver metastasis, and up to 30 percent of patients are likely to eventually develop liver metastasis within five years after rectal cancer diagnosis (16, 17).

Treatment

Depending on whether a patient suffers from synchronous or metachronous rectal cancer metastasis and whether the metastases are liver-limited or systemic, different treatment pathways are available. Patients with synchronous liver metastasis do often require complex and synchronized management of both the rectal tumor and the metastasis (15). Contrastingly, patients who have undergone curative resection of the primary rectal tumor before they are diagnosed with metachronous liver metastasis can receive metastasis-focused treatments (15). If the rectal cancer metastasis is systemic, chemotherapy is currently the main treatment (15).

There are currently three different strategies to surgically remove synchronous rectal cancer liver metastases. The “classic approach” comprises a primary resection of the rectal tumor, followed by adjuvant chemotherapy and subsequent liver resection. The “liver-first approach” implies that the liver metastases are removed before the rectal resection**.** The third available strategy is simultaneous liver and rectal resection (18, 19). The choice of method is debatable. The rationale for the classic approach is that the rectal tumor is usually the main cause of symptoms and subsequent metastasis, suggesting that the primary rectal tumor should be removed first (18, 19). Contrastingly, some studies suggest that liver metastasis is the likeliest course of subsequent systemic metastases, thus supporting liver surgery as the first operative intervention (18, 19). The synchronous approach has the advantage of removing the macroscopic cancer burden in one session. However, although simultaneous surgery may reduce the total blood loss and shorten the total time of hospitalization, a combination of complex liver and bowel surgery is more likely to result in considerable morbidity (18, 19).

The amount of liver parenchyma that can be safely resected depends on different factors, such as age and comorbidity. In healthy adult individuals, up to 80 percent of the liver can be resected (20). Patients with chemotherapy-induced liver injuries require a residual liver volume of approximately 30 percent, and patients with liver cirrhosis require at least 40 percent (20). Before surgery, neoadjuvant chemotherapy could shrink the metastases to increase the chances for a complete and curative resection while also limiting the amount of liver parenchyma that has to be resected as well as reducing the number of intrahepatic micrometastases (21).

Non-resectional ablative treatments are also available for the treatment of liver metastases. Ablative treatments use energy sources for heating up the metastases to induce coagulative oncosis (15). The most commonly used ablative treatments utilize radio frequencies (radiofrequency ablation) or microwave energy and can be used as alternatives to surgery or in adjunction to it (15, 22). However, because of various technical circumstances, ablative treatments are not efficient enough for treatment of all cases of liver metastasis (23).

Prognosis

Rectal cancer mortality is predominantly determined by liver metastasis (24). Numerous factors, including the location, size, number, and level of differentiation of the metastases as well as N-status and primary tumor resection status, are related to the patient survival rates (24). The overall 5-year survival rate for patients with colorectal cancer and synchronous liver metastasis is poor without treatment but can reach up to at least 46 percent if the metastases are surgically removed (15, 25).

Radiological Assessment of the Liver

According to the current Swedish national guidelines, adequate preoperative cross-sectional imaging of the liver is recommended to examine possible liver metastasis in patients with rectal cancer before any treatment decisions are made. For this purpose, the guidelines specifically recommend a contrast-enhanced computed tomography (CT). If a patient, for some reason, cannot be adequately examined using a contrast-enhanced CT of the liver, liver metastasis can also be evaluated using magnetic resonance imaging (MRI), contrast-enhanced ultrasonography, or a combination of positron emission tomography and CT (PET-CT) (4). However, PET-CT is rarely used to primarily examine liver metastasis.

Computed tomography

CT is a non-invasive procedure that use ionizing x-ray photons to produce cross-sectional images of the body. Because internal structures of similar densities sometimes can be difficult to distinguish, contrast agents are often added to many CT protocols to enhance different tissues and fluids on the resulting images (26, 27). The current Swedish national guidelines recommend the usage of an intravenously administered low-osmolar contrast medium when examining the liver for rectal cancer metastasis (4). A non-contrast enhanced CT can only in some cases confirm liver metastasis; however, metastatic disease cannot be ruled out in the absence of intravenous contrast agents.

Magnetic resonance imaging

Similar to CT, MRI is a non-invasive procedure that can be used to visualize internal structures. An MRI utilizes a strong magnetic field and radiofrequency waves that interact with tissues to produce images of the body in varying shades of grey. During the examination, the magnetic field aligns hydrogen nuclei that normally are randomly distributed within tissues. Radiofrequency pulses excite the aligned hydrogen nuclei, which in turn, depending on tissue characteristics, relax into their original state of thermal equilibrium while emitting new radiofrequency pulses that can be measured, calculated, and presented as cross-sectional images. Using a compilation of different radiofrequency pulses, sequences, and contrast agents, information from molecules in the body, particularly from soft tissues, are translated into highly detailed images (28).

An MRI protocol is composed of a set of different sequences to display tissues and pathological processes as adequately as possible. When examining the liver regarding rectal cancer metastasis, the current Swedish national guidelines recommend that an MRI includes

T1-, T2-, and diffusion-weighted sequences as well as T1-weighted sequences enhanced with intravenous (preferably liver-specific) gadolinium contrast agents (4). T1-weighted images present the longitudinal relaxation of the hydrogen nuclei. T2-weighted images present the corresponding transversal relaxation. As results, fluids show up darker on T1-weighted images and contrastingly brighter on T2-weighted images (28). The addition of gadolinium contrast agents to the T1-weighted sequences shortens the T1-relaxation. Intravenously administered gadolinium contrast agents will, therefore, facilitate the imaging of blood vessels. Apart from the regular extracellular gadolinium contrast agents, there are also liver-specific gadolinium agents that can be absorbed by hepatocytes to enhance the imaging of the liver (28). Finally, diffusion-weighted imaging detects the random movements and free diffusion of water molecules both intra- and extracellularly as well as across cell membranes. In highly cellular tissues, such as tumors, the apparent diffusion of water is often impeded, which shows up on diffusion-weighted images (28).

Magnetic resonance imaging or computed tomography as a preoperative liver examination

According to a randomized controlled trial comparing preoperative contrast-enhanced CT with diffusion-weighted MRI of the liver in patients with rectal cancer, the per-patient sensitivity/specificity was 50/100 percent for contrast-enhanced CT and up to 100/100 percent for diffusion-weighted MRI. Furthermore, the per-lesion sensitivity was 17 percent for contrast-enhanced CT and 89 percent for diffusion-weighted MRI (25). The proposition that MRI has superior diagnostic accuracy for liver metastases compared with contrast-enhanced CT is further supported in larger meta-analyses and another randomized controlled trial (29-31). Additionally, potential cost-effectiveness is associated with MRI as a replacement for contrast-enhanced CT, according to an Australian study comparing the incremental costs relative to the incremental benefits of contrast-enhanced CT and MRI for diagnosis of liver metastasis in patients with colorectal cancer (32). Still, the current Swedish national guidelines recommend, as mentioned, a contrast-enhanced CT as the routine preoperative examination of the liver before making treatment decisions at multidisciplinary team conferences regarding patients who are newly diagnosed with rectal cancer (4).

Based on the fact that other studies have shown a higher sensitivity/specificity for MRI compared with contrast-enhanced CT regarding liver metastases, the Sahlgrenska University Hospital has implemented a routine that generally deviates from the current Swedish national guidelines. Rather than examining the pelvic organs with an MRI and the liver with a contrast-enhanced CT, the Sahlgrenska University Hospital use a routine of an adapted and combined MRI protocol of the pelvic region and the upper abdomen (including the liver) (33). The added liver examination is a condensed liver MRI protocol focusing on diffusion-weighted imaging. The intention is to provide a more accurate rectal cancer staging with fewer supplementary liver examinations during the primary workup before treatment for rectal cancer. Thereby, the aim is to shorten the time between diagnosis and treatment initiations. However, no studies have been performed to substantiate this hypothesis.

SPECIFIC OBJECTIVES

The purpose of this study was to compare the efficacy of MRI with contrast-enhanced CT as the index examination of the liver in patients with a newly diagnosed rectal cancer.

Hypothesis

Our hypothesis is that, compared with contrast-enhanced CT, MRI as the index examination of the liver results in a reduced need of supplementary liver examinations before treatment for rectal cancer. Furthermore, we hypothesize that MRI as the index examination of the liver results in a larger proportion of patients who are diagnosed with liver metastases and also in a larger proportion of patients who undergo liver surgery within 18 months after the index liver examination.

Primary Objective

To compare MRI with contrast-enhanced CT as the index examination of the liver regarding the proportion of patients who underwent supplementary radiological liver examinations before treatment for rectal cancer.

Secondary Objectives

To compare MRI with contrast-enhanced CT as the index examination of the liver regarding:

1. the proportion of patients who were diagnosed with liver metastases, and
2. the proportion of patients who were treated with liver resection and/or ablation for liver metastases within 18 months after the index examination of the liver.

MATERIALS AND METHODS

Study Design

This was a retrospective study using clinical data from patients who were diagnosed with rectal cancer at the Sahlgrenska University Hospital and within the NU Hospital Group in the Region Västra Götaland, Sweden.

The inclusion criteria were patients with a rectal cancer diagnosis, C20.9 (ICD-10), that was registered at the Sahlgrenska University Hospital or within the NU Hospital Group before 2015-12-31. The exclusion criteria included missing or inadequate routine preoperative MRI or contrast-enhanced CT of the liver and local rectal tumor excisions.

Study population

Assuming that the proportions of patients who underwent supplementary radiological liver examinations before the treatment for rectal cancer were 15 percent after an index contrast-enhanced CT and 5 percent after an index MRI, a two-sided t-test at 5 percent level with 80 percent power requires a sample size of 138 evaluable patients in each group (n = 276). This estimation was based on clinical experience.

The Swedish Rectal Cancer Register was established in 1995 for registration of data on rectal cancers in Sweden. All Swedish hospitals report to the register (34). The ColoRectal Cancer Register combines data from both patients with colon cancers and patients with rectal cancer.

Lists of patients were assembled by working backwards through the Regional ColoRectal Cancer Register from 2015-12-31 until 320 patients with rectal cancer were included (160 patients from the Sahlgrenska University Hospital and 160 patients from the NU Hospital

Group). Hence, cohorts of patients who were diagnosed with rectal cancer between 2014-12-08–2015-12-31 and 2013-12-06–2015-12-31 at the Sahlgrenska University Hospital and the NU Hospital Group respectively were generated. Each patient was then assigned a specific study ID before the study population was divided into two groups depending on which radiological method that had been used for the index examination of the liver (MRI or contrast-enhanced CT), regardless of at what hospital the patients had been treated.

Data Collection

Data were collected from three different sources: [1] the Regional ColoRectal Cancer Register, [2] hospital records, including radiology reports, and [3] re-evaluations of selected index liver examinations as part of this study.

Data concerning age, gender, body mass index, hospital affiliation, time for rectal cancer diagnosis, time for oncological treatments, type of oncological treatments, clinical TNM stage, and American Association of Anesthesiologists classification were retrieved from the Regional ColoRectal Cancer Register.

All relevant data between the time for the index liver examination and 2017-12-31 were collected from hospital records and radiology reports using a customized case report form. Such data included dates for index and supplementary liver examinations and outcomes regarding liver metastasis, dates for multidisciplinary team conferences (MDT), and dates and the Nordic Medico-Statistical Committee (NOMESCO) codes for any conducted liver surgery. Radiology reports were categorized as either conclusive or inconclusive depending on whether liver metastasis had been confirmed/ruled out (conclusive), or neither (inconclusive).

As part of this study, all index liver examinations that resulted in inconclusive radiology reports regarding liver metastasis were re-evaluated by two radiologists (P. Kälebo and P. Nilsson). Jointly, they assessed the examinations regarding liver metastasis and registered their findings in the database. However, the re-evaluations did not affect the outcomes of this study but were included to possibly provide a deeper understanding of the results. These re-evaluations were performed three to four years after the writing of the original radiology reports and did in no way affect the clinical management of the patients.

Because the date for the first treatment decision at a multidisciplinary conference would have been the final step in the workup before rectal cancer treatment, it might have been an interesting variable to consider. However, these dates were difficult to collect and therefore not part of this study.

Statistical Methods

Data processing

The first liver examination (MRI or contrast-enhanced CT) that was used to examine the liver regarding rectal cancer metastasis before treatment was defined as the index liver examination. If a patient had undergone supplementary radiological examinations, which resulted in radiology reports indicating that the liver had been evaluated regarding rectal cancer metastasis, these examinations were sorted into two categories:

1. "Liver examinations", including MRI, contrast-enhanced CT, contrast-enhanced ultrasonography; and
2. "Other examinations", including other evaluable examinations of the liver, such as CT colonography.

Only supplementary examinations of the first group were analyzed in this study.

Further data processing was conducted as follows: [1] Synchronous liver metastasis was defined as radiologically confirmed liver metastasis within six months after the date of rectal cancer diagnosis. Liver metastasis that was detected more than six months after diagnosis was defined as metachronous. [2] The clinical TNM stages of the rectal cancers were translated into stages I–IV based on the Union for International Cancer Control (UICC) *TNM classification of malignant tumors* (10). [3] Patients who did not undergo rectal resection surgery, who were treated with stents or stomas alone, or who received oncological treatments in palliative settings were considered as given palliative treatment. [4] The date for treatment initiation was derived from the first date of neoadjuvant treatments and rectal/liver surgery. Regarding the palliative patients who did not receive any of these treatments, the dates for treatment initiations were derived from the date of the multidisciplinary team conference (MDT) at which the first treatment decision was likely to have been made.

Only data from within 18 months after the index liver examination were analyzed. The timeframe of 18 months was chosen in order for this study to also include the 12-month follow-up radiological liver examination even when some of the included patients had undergone longer neoadjuvant treatments before surgery.

Variable analysis

Two different index examinations of the liver were compared: [1] MRI and [2] contrast-enhanced CT. The primary outcome involved a comparison regarding the proportion of patients who underwent supplementary liver examinations after the index examination of the liver before treatment for rectal cancer. The comparison also involved two secondary outcomes: [1] the proportion of patients who were diagnosed with liver metastases, and [2] the proportion of patients who were treated with liver resection or ablation within 18 months after the index liver examination.

IBM SPSS 24.0 was used for statistical calculations. An alpha level of 0.05 was used, and differences resulting in p-values of less than 0.05 were considered statistically significant. The demographic analysis was performed using Student's t-test or Mann-Whitney U-test for continuous variables and Pearson's chi-squared test or Fisher's exact test for categorical variables. The primary and secondary outcomes were analyzed using Pearson's chi-squared test.

ETHICAL ASPECTS

Patients were not contacted, and only already registered information was included in this study. Data of this kind are considered to have a small impact on personal integrity, and the cohort size was such that tracing any of the results to an individual patient is not possible. Thus, in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects (35), the requirement of informed consent was waived. Once the data collection was completed, the database was anonymized by the removal of all personal identification numbers.

This project received approval by the Regional Ethical Review Board in Gothenburg (Dnr: 352-17) and was registered at clinicaltrials.gov (NCT03463616).

RESULTS

After examining the lists of the 320 patients included from the Regional ColoRectal Cancer Register, 46 patients were excluded from the analyses (*Figure 1*).

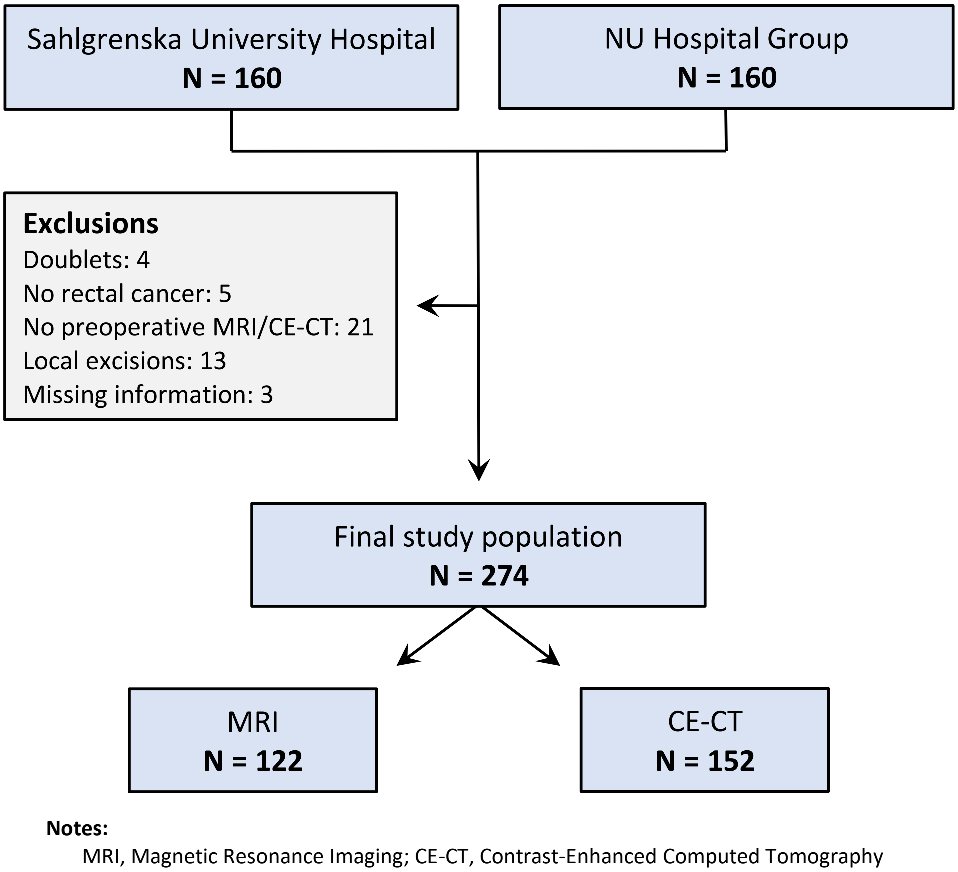

Figure 1. Flow chart of the study population. Some patients fulfilled more than one exclusion criterion.

39 patients fulfilled at least one of the exclusion criteria: 5 patients did not have rectal cancer, 21 patients had not undergone an adequate routine preoperative MRI or contrast-enhanced CT of the liver, and 13 patients had undergone local excisions of rectal tumors. Furthermore, 7 non-evaluable patients were identified: 4 cases were doublets of already included patients and 3 patients were missing essential register information. The remaining 274 patients were subdivided into two groups with respect to whether MRI or contrast-enhanced CT was used as the index examination of the liver (122 patients with index MRI, 152 patients with index contrast-enhanced CT). Demographics and baseline patient features are presented in *Table 1*.

Table 1. Demographics of 274 patients with rectal cancer.

Characteristics	Type of index liver examination		
	MRI[a] (N = 122)	CE-CT[b] (N = 152)	Total (N = 274)
Male — no. (%)	81 (66)	90 (59)	171 (62)
Age at diagnosis* — yr (mean±SD)	67±13	71±10	69±12
Range (min–max)	25–92	30–93	25–93
Body Mass Index — kg/m² (mean±SD)	25±4	26±4	26±4
Range (min–max)	18–34	17–36	17–36
Missing data — no. (%)	21 (17)	42 (28)	63 (23)
Hospital** — no. (%)			
Sahlgrenska University Hospital	121 (99)	18 (12)	139 (51)
NU Hospital Group	1 (1)	134 (88)	135 (49)
Clinical UICC stage** — no. (%)			
Stage I	31 (25)	9 (6)	40 (15)
Stage II	36 (30)	21 (14)	57 (21)
Stage III	29 (24)	86 (56)	115 (42)
Stage IV	19 (15)	30 (20)	49 (18)
Missing data	7 (6)	6 (4)	13 (4)
American Society of Anesthesiologists classification — no. (%)			
I: Healthy	15 (12)	17 (11)	32 (12)
II: Mild systemic disease	68 (55)	68 (45)	136 (50)
III: Severe systemic disease	19 (16)	25 (16)	44 (16)
IV: Severe life-threatening systemic disease	1 (1)	3 (2)	4 (1)
Missing data	19 (16)	39 (26)	58 (21)
Multidiciplinary team conference — no. (%)			
Yes	122 (100)	152 (100)	274 (100)
Days from diagnosis to treatment initiation[a]			
Median no. (IQR)	54 (42–75)	56 (44–70)	56 (43–70)
Neoadjuvant treatment — no. (%)			
Yes	66 (54)	87 (57)	153 (56)
No	42 (34)	58 (38)	100 (36)
Missing data	14 (12)	7 (5)	21 (8)
Therapeutic approach† — no. (%)			
Curative	100 (82)	108 (71)	208 (76)
Palliative	19 (16)	37 (24)	56 (20)
Missing data	3 (2)	7 (5)	10 (4)

[a]Magnetic resonance imaging
[b]Contrast-enhanced computed tomography
†Treatment initiations represent the start of neoadjuvant treatment or surgery, or, if missing, the first treatment decision at MDT.
*Student's t-test / **Pearson's chi-squared test resulted in a two-sided p-value < 0.05.

The two groups were similar with respect to gender, body mass index, American Society of Anesthesiologists classification, days from diagnosis to treatment, the reception of neoadjuvant treatment, and therapeutic approach (curative or palliative) (*Table 1*). All patients were discussed at multidisciplinary team conferences (MDT). Statistically significant differences were discovered regarding age at diagnosis, hospital affiliation, and clinical tumor stage.

Table 2. Radiology report results from index liver examinations regarding liver metastasis.

Index liver examinations — no. (%)	Type of index liver examination MRI[a] (N = 122)	CE-CT[b] (N = 152)	Total (N = 274)	*P-value*
Results				0.011
Liver metastasis	14 (12)	14 (9)	28 (10)	
No liver metastasis	103 (84)	115 (76)	218 (80)	
Inconclusive	5 (4)	23 (15)	28 (10)	

[a]Magnetic resonance imaging

[b]Contrast-enhanced computed tomography

In the MRI group, 12 percent of the patients were diagnosed with liver metastasis at the index examination of the liver, compared with 9 percent of the patients in the contrast-enhanced CT group. Furthermore, compared with MRI, contrast-enhanced CT as the index examination of the liver resulted in an almost four times larger proportion of inconclusive radiology reports regarding liver metastasis (*Table 2*).

Table 3. Patients who underwent supplementary liver examinations before treatment for rectal cancer.

Supplementary liver examinations before treatment initiation† — no. (%)	Type of index liver examination MRI[a] (N = 122)	CE-CT[b] (N = 152)	Total (N = 274)	*P-value*
Total no. of patients who underwent supplementary liver examinations	16 (13)	23 (15)	39 (14)	0.635
No. of supplementary liver examinations				0.652
0	106 (87)	129 (85)	235 (86)	
1	14 (11)	17 (11)	31 (10)	
2	1 (1)	4 (2)	5 (1)	
3	0	1 (1)	1 (1)	
4	0	1 (1)	1 (1)	
5	1 (1)	0	1 (1)	

†Treatment initiation represent the start of neoadjuvant treatment or surgery, or, if missing, the first treatment decision at MDT.

[a]Magnetic resonance imaging

[b]Contrast-enhanced computed tomography

The proportions of patients who underwent supplementary liver examinations (MRI, contrast-enhanced CT, or contrast-enhanced ultrasonography) before treatment were 13 percent in the MRI group and 15 percent in the contrast-enhanced CT group. In both groups, these patients underwent a median number of one supplementary liver examination. Altogether, 21 and 32 extra liver examinations were performed on patients the MRI and contrast-enhanced CT groups respectively (*Table 3*).

Table 4. Patients with inconclusive radiology reports from index examinations and the proportion of those who underwent supplementary examinations before treatment for rectal cancer.

Inconclusive index examinations — no. (%)	Type of index liver examination			*P-value*
	MRI[a] (N = 122)	CE-CT[b] (N = 152)	Total (N = 274)	
Total	5 (4)	23 (15)	28 (10)	0.003
Resulting in supplementary examinations	2 (40)	10 (44)	12 (43)	

[a]Magnetic resonance imaging
[b]Contrast-enhanced computed tomography

Contrast-enhanced CT resulted in a significantly larger proportion of patients with inconclusive radiology reports from index examinations of the liver compared with MRI, but a large number of these patients never underwent any supplementary liver examinations before treatment for rectal cancer (*Table 4*).

All 28 inconclusive radiology reports from index examinations were re-evaluated by two radiologists as part of this study. These re-evaluations resulted in 2 index MRI and 13 index contrast-enhanced CT examinations that were still reported as inconclusive regarding liver metastasis. In real life, out of these individuals with consistently inconclusive index examinations of the liver, 1 out of 2 patients in the MRI group and 6 out of 13 patients in the contrast-enhanced CT group underwent supplementary liver examinations before treatment for rectal cancer.

Table 5. Patients who developed liver metastases within 18 months after the index examination.

Liver metastasis — no. (%)	Type of index liver examination			*P-value*
	MRI[a] (N = 122)	CE-CT[b] (N = 152)	Total (N = 274)	
Total	20 (16)	27 (18)	47 (17)	0.765
Synchronous	17 (85)	23 (85)	40 (85)	
Metachronous	3 (15)	4 (15)	7 (15)	

[a]Magnetic resonance imaging
[b]Contrast-enhanced computed tomography

The proportion of patients who developed liver metastases from rectal cancer within 18 months after the index liver examination was 16 percent in the MRI group and 18 percent in the contrast-enhanced CT group. Altogether, 40 patients developed synchronous liver metastases and 7 patients developed metachronous liver metastases. The difference in incidences of liver metastasis between the two groups was not statistically significant (*Table 5*).

Table 6. Patients who were treated with surgery.

Surgery† — no. (%)	Type of index liver examination MRI[a] (N = 122)	CE-CT[b] (N = 152)	Total (N = 274)	*P-value*
Any surgery				0.011
Yes	107 (88)	115 (76)	222 (81)	
No	15 (12)	37 (24)	52 (19)	
Rectal surgery				0.014
Yes	106 (87)	114 (75)	220 (80)	
Anterior resection, incl. Hartmann's procedure	56 (53)	66 (58)	122 (55)	
Abdominoperineal excision	39 (37)	48 (42)	87 (40)	
Other	11 (10)	0	11 (5)	
Liver surgery				0.016
Yes	10 (8)	3 (2)	13 (5)	
Resection	5 (50)	1 (33)	6 (46)	
Ablation	1 (10)	1 (33)	2 (15)	
Both	4 (40)	1 (34)	5 (39)	

†Within 18 months from the index liver examination.
[a]Magnetic resonance imaging
[b]Contrast-enhanced computed tomography.

Surgery was more commonly performed on patients in the MRI group. 88 percent of the patients in the index MRI group and 76 percent of patients in the contrast-enhanced CT group underwent rectal and/or liver surgery within 18 months from the index liver examination. In the MRI group, rectal surgery was performed on 87 percent of the patients, compared with 75 percent in the contrast-enhanced CT group. In both groups, anterior resection (including Hartmann's procedure) was the most commonly performed procedure for rectal surgery. An almost four times larger proportion of patients in the MRI group compared with the contrast-enhanced CT group underwent liver surgery within 18 months after the index examination (*Table 6*).

DISCUSSION

Whether an MRI or a contrast-enhanced CT was used for the index examination of the liver among patients with newly diagnosed rectal cancer, there were no significant differences in the proportions of patients who underwent supplementary liver examinations before treatment for rectal cancer or were diagnosed with liver metastases throughout this study. Liver surgery was more often performed on the patients in the MRI group.

Other studies have advocated a higher sensitivity and specificity for MRI regarding the diagnosis of liver metastasis (25, 29-31). It was, therefore, not surprising that contrast-enhanced CT appeared to result in a larger proportion of inconclusive radiology reports. Consequently, it seemed reasonable that a larger proportion of the patients who underwent an index contrast-enhanced CT should have been subjected to supplementary liver examinations to either confirm or rule out concurrent liver metastasis before treatment for rectal cancer. One possible reason as to why this rationale did not apply in this study could be that some radiologists may have preferred to give inconclusive radiology reports in case there was the slightest doubt regarding possible liver metastasis. If so, it seems likely that these examinations were re-evaluated at multidisciplinary team conferences, which, despite the original radiology report, may have resulted in liver metastasis being either confirmed or ruled out. Subsequently, there would have been no further need for additional liver examinations before initiating rectal cancer treatments, even though the original radiology report suggested otherwise.

Demographics were expected to differ significantly regarding the patients' hospital affiliations, since the Sahlgrenska University Hospital used routine MRI for the index examination of the liver in patients with newly diagnosed rectal cancer, whereas the NU

Hospital Group used routine contrast-enhanced CT for the same purpose. This implies that the majority of the patients in the MRI group were managed at the Sahlgrenska University Hospital and that the majority of the patients in the contrast-enhanced CT group were managed within the NU Hospital Group. However, demographics further suggested that the patients who were examined using an index contrast-enhanced CT were both older and initially diagnosed with more advanced rectal cancers.

People living in metropolitan areas may have easier access to hospitals than patients in rural areas. Because the Sahlgrenska University Hospital had a catchment area that consisted of a larger metropolitan area, whereas the catchment area for the NU Hospital Group consisted of more rural areas of the Region Västra Götaland, Sweden, patients who were managed at the Sahlgrenska University Hospital might have sought health care at an earlier stage of their disease. It is, therefore, possible that the differences in age and cancer stage between the groups resulted from a longer patients' delay among the patients who were managed within the NU Hospital Group due to differences in the accessibility of healthcare. Moreover, these differences in demographics could partially explain why patients in the contrast-enhanced CT group were less treated with liver surgery than patients in the MRI group, even though there was no difference in the incidence of liver metastasis between the two groups.

Another possible explanation to why liver surgery was more often performed on patients in the MRI group is based on the fact that all liver surgery within the Region Västra Götaland was carried out at the Sahlgrenska University Hospital. The better accessibility to liver surgeons may, therefore, have made it easier for patients who were primarily managed at the Sahlgrenska University Hospital to receive a referral for liver surgery compared with patients who were primarily managed within the NU Hospital Group. In conclusion, not only was hospital affiliation associated with the method used for the index examination of the liver, but it was also likely a confounding factor.

There are no previous studies to compare these results with. This study provides a good foundation to base future research on.

Strengths and Limitations

One strength was that all patients who had been diagnosed with rectal cancer at the Sahlgrenska University Hospital or within the NU Hospital Group during a specific period were included in this study unless they met any of the exclusion criteria. Further strengths were that there was no patient selection, basic clinical data were gathered from a register with high validity, and all patient records were accessible. The case report form was designed before initiating any data collections from hospital records. The actual retrieval of data was performed by one person (M. Utterberg).

One limitation was the retrospective design. Further limitations were that the power estimation was based on clinical experience and that the patient cohorts may have differed, in some respects, based on hospital affiliation. Furthermore, additional MRI, contrast-enhanced CT, or contrast-enhanced ultrasonography that were used primarily to visualize other pathological processes occurring with rectal cancer might sometimes also have resulted in statements regarding liver metastasis. Therefore, the total number of liver examinations may have been slightly exaggerated in both groups.

Conclusions

The usage of MRI for the index examination of the liver among patients with newly diagnosed rectal cancer did not show any clinical advantage over contrast-enhanced CT. Thus, this study gives no reason to change the current Swedish national guidelines regarding the recommendation of a contrast-enhanced CT of the liver as standard workup before treatment for rectal cancer.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Magnetkamera eller skiktröntgen av levern vid utredning av ändtarmscancer?

Examensarbete 30 HP, läkarprogrammet

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Handledare: Eva Haglind

Avdelningen för kirurgi, Sahlgrenska Akademin, Göteborg 2018

I takt med att vi människor blir både fler och äldre beräknas antalet cancerfall världen över att öka, enligt en studie från Världshälsoorganisationen (WHO). I dagsläget drabbar ändtarmscancer årligen ungefär 2 000 svenskar och är den nionde vanligaste cancerformen i Sverige. Symtomen är till stor del ospecifika, men drabbade patienter talar ofta om förändrade avföringsvanor, ofrivillig viktnedgång och ibland även blödningar från ändtarmen.

Sedan 2016 finns det nationella riktlinjer för en förbestämd och strukturerad vårdprocess för att vid både misstänkt och konstaterad ändtarmscancer begränsa skillnaderna i hur patienter utreds och behandlas mellan alla Sveriges sjukhus. Eftersom levern är det organ som oftast drabbas vid spridning (metastasering) av ändtarmscancer rekommenderas att dessa patienter bland annat genomgår en skiktröntgenundersökning av levern. Då metastasering kan påverka både prognos och behandlingsmetod är det viktigt att veta om en patient har levermetastaser eller inte innan behandling påbörjas.

Inom NU-sjukvården i norra delarna av Västra Götalandsregionen undersöks patienter med ändtarmscancer enligt de nationella riktlinjerna. En del tidigare studier har dock visat att magnetkamera kan vara bättre än skiktröntgen på att upptäcka levermetastaser. Därför avviker Sahlgrenska Universitetssjukhuset i Göteborg från de nationella riktlinjerna och erbjuder istället sina patienter en magnetkameraundersökning av levern. Denna avvikelse syftar till att minska andelen patienter som behöver genomgå extra leverundersökningar innan ett behandlingsbeslut kan fattas och på så vis också förkorta tiden mellan diagnos och behandlingsstart. Därmed har denna studie haft för avsikt att jämföra magnetkamera och skiktröntgen vid den första leverundersökningen bland patienter med nydiagnostiserad ändtarmscancer.

Totalt analyserades 274 patienter som diagnosticerats med ändtarmscancer vid Sahlgrenska Universitetssjukhuset eller inom NU-sjukvården. Oavsett om magnetkamera eller skiktröntgen använts för att initialt undersöka levern var det ingen skillnad i andelen patienter som behövde genomgå extra leverundersökningar innan behandling kunde påbörjas. Det var heller ingen skillnad i andelen patienter som under studiens gång diagnostiserats med levermetastaser. Däremot var det vanligare med leverkirurgi bland patienterna som initialt undersökts med magnetkamera.

Majoriteten av de patienter som initialt genomgått en magnetkameraundersökning av levern hade diagnosticerats med ändtarmscancer vid Sahlgrenska Universitetssjukhuset, medan större delen av de patienter som genomgått en skiktröntgen hade diagnosticerats inom NU-sjukvården. Därför är det möjligt att patienternas sjukhustillhörighet kan ha påverkat studiens resultat. För det första finns alla regionens leverkirurger vid Sahlgrenska Sjukhuset, vilket kan ha påverkat tillgången på leverkirurgi. För det andra noterades att de patienter som genomgått skiktröntgen, och alltså i stor utsträckning hanterats inom NU-sjukvården, var både äldre och oftare hade en mer avancerad ändtarmscancer. Detta skulle kunna bero på att tillgången på vård kan vara mer begränsad på landsbygden än i storstäderna och att patienterna som undersökts med skiktröntgen därmed sökt vård i ett senare skede än de som undersökts med magnetkamera. Svårare cancerstadier och därmed försämrade prognoser bland patienterna i gruppen som undersökts med skiktröntgen kan ha lett till att de i större utsträckning fått avstå från leverkirurgi.

Sammanfattningsvis kunde inte denna studie påvisa några kliniska fördelar med att välja magnetkamera över skiktröntgen i samband med den initiala leverundersökningen vid nydiagnostiserad ändtarmscancer. Alltså finns i dagsläget ingen anledning att revidera de idag rådande riktlinjerna i detta avseende.

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