PREOPERATIVE IMAGING OF THE CHEST IN THE STAGING OF PATIENTS WITH RECTAL CANCER

Anissa Ourtani
Promotor: Prof. Dr. Wim Ceelen

Dissertation presented in the 2nd Master year in the programme of MASTER OF MEDICINE IN MEDICINE
PREOPERATIVE IMAGING OF THE CHEST IN THE STAGING OF PATIENTS WITH RECTAL CANCER

Anissa Ourtani
Promotor: Prof. Dr. Wim Ceelen

Dissertation presented in the 2nd Master year in the programme of
MASTER OF MEDICINE IN MEDICINE
"The author and the promotor give the permission to use this thesis for consultation and to copy parts of it for personal use. Every other use is subject to the copyright laws, more specifically the source must be extensively specified when using results from this thesis."

Date: May 3, 2012

Anissa Ourtani

Prof. Dr. Wim Ceelen
Foreword

While working on this dissertation, I realized that writing something particular is a long and intensive process. At the same time, it became clear to me that I would not have been able to create this work without the help of other people. Therefore, I want to take this opportunity to thank everyone who supported me with this research.

In the first instance I want to thank especially my promotor, Prof. Dr. Wim Ceelen, for his precious time and for inspiring me and helping me during the entire course. With his unvaluable knowledge on the subject of my thesis and his extensive experience on research and statistics, he taught me things that were crucial to obtain the goals of this thesis and he really made my interest in scientific research grow.

Special thanks as well to Inge Vandenbroucke and Saskia De Groote, the two wonderful study nurses at the Department of the Gastrointestinal Surgery at the Ghent University Hospital. They learned me how to work with the patients’ database and were very helpful with all kind of administrative and practical affairs.

And last, but not least, I would like to thank my parents and my brother, who gave me their infinite support during my medical studies, and specifically during the period of approximately two years in which I have achieved my research. Without them, nothing would have been possible at all in the first place.

Anissa
Table of contents

List of figures.................................................................................................................................................................I

List of tables........................................................................................................................................................................II

1. Abstract (English)............................................................................................................................................................1

1. Abstract (Dutch)..............................................................................................................................................................3

2. Introduction........................................................................................................................................................................5

2.1. General introduction..................................................................................................................................................5

2.1.1. Influence of metastases on survival.................................................................................................................5

2.1.2. Sensitivity and specificity of chest CT and chest X-ray..................................................................................6

2.1.3. Guidelines for the use of preoperative imaging by chest CT and/or X-ray.......................................................6

2.1.4. Difference in incidence of lung metastases between colon and rectal cancer..............................................7

2.1.5. Purpose of this study............................................................................................................................................8

2.2. Types of colorectal cancer.......................................................................................................................................8

2.3. Epidemiology of colorectal cancer.........................................................................................................................9

2.3.1. Epidemiology of colorectal cancer: Belgium.....................................................................................................9

2.3.2. Epidemiology of colorectal cancer: Global........................................................................................................11

2.4. Symptoms of colorectal cancer............................................................................................................................13

2.5. Risk factors for colorectal cancer..........................................................................................................................13

3. Materials en methods ..................................................................................................................................................15

3.1. Literature study .......................................................................................................................................................15

3.1.1. Current guidelines regarding management of rectal cancer............................................................................17

3.1.1.1. Preoperative guidelines regarding rectal cancer..........................................................................................18

3.1.1.2. Staging of rectal cancer (TNM classification).................................................................................................20

3.1.1.3. Therapeutic guidelines regarding rectal cancer.............................................................................................23

3.1.1.4. Postoperative guidelines (follow-up) regarding rectal cancer.................................................................25
3.2. Patient study

3.2.1. Definition and criteria

3.2.2. Description of how the data was collected

4. Results

4.1. Population characteristics

4.1.1. Demographic data

4.1.2. Number and localization of metastases following rectal cancer

4.1.3. Survival analysis

4.2. Chest CT and X-ray

4.2.1. Presence or absence of lung lesions on imaging of the chest

4.2.2. Preoperative versus postoperative chest CT and X-ray imaging

4.2.3. Diagnostic characteristics of chest CT and X-ray imaging for diagnosing lung metastases following rectal cancer

4.3. cTNM and pTNM

4.3.1. Observations

5. Discussion

5.1. Summary of the most important results

5.2. Diagnostic characteristics of chest CT/X-ray

5.3. Differences in results of the use of chest CT and chest X-ray

5.4. Difference in incidence of lung metastases between colon cancer and rectal cancer

5.5. Shortcomings of this study

5.6. Considerations

6. Conclusion

7. References
List of figures

Fig. 1: Trends in incidence of colorectal cancer in Belgium.................................................................10

Fig. 2: The 20 most common diagnosed cancers worldwide.............................................................11

Fig. 3: Incidence and mortality rates in the regions of the world (female) ...........................................12

Fig. 4: Incidence and mortality rates in the regions of the world (male) .............................................12

Fig. 5: Flowchart of selection of articles (preoperative imaging of the chest in staging (colo-)rectal cancer)............................................................................................................................................16

Fig. 6: Flowchart of selection of articles (higher incidence of lung metastases in rectal cancer compared to colon cancer)..............................................................................................................................17

Fig. 7: Diagnosis and staging of rectal cancer......................................................................................19

Fig. 8: Neoadjuvant therapy guidelines regarding resectable rectal cancer.........................................24

Fig. 9: Adjuvant therapy guidelines regarding rectal cancer...............................................................24

Fig. 10: Postoperative guidelines regarding rectal cancer ..................................................................27

Fig. 11: Flowchart: exclusion of patients in this study.........................................................................28

Fig. 12: Summary: number and localization of metastases following rectal cancer in this study........32

Fig. 13: Survival analysis (after group staging of cTNM) _ Kaplan Meier curve.................................33

Fig. 14: Survival analysis (after group staging of pTNM) _ Kaplan Meier curve.................................34

Fig. 15: Survival analysis of the patients diagnosed with lung metastases in this study _ Kaplan Meier curve..................................................................................................................................................35
**List of tables**

**Table 1:** Guidelines regarding preoperative imaging of the chest (CT/X-ray) in staging rectal cancer ...7

**Table 2:** Incidence of lung metastases in colon and/or rectal cancer per article used in this study........8

**Table 3:** Number of new cases of colorectal cancer in Belgium in 2004..................................................9

**Table 4:** Number of new cases of colorectal cancer in Belgium in 2007..................................................10

**Table 5:** 5-year survival rate and median survival time of the patients per group stage of cTNM ......34

**Table 6:** 5-year survival rate and median survival time of the patients per group stage of pTNM...........35

**Table 7:** 5-year survival rate and median survival time of the patients diagnosed with lung metastases........................................................................................................................................36

**Table 8:** Number of lung lesions protocolled by the radiologist as ‘lung metastases’, ‘indeterminate lung lesions’ and ‘no lung metastases’........................................................................................................................................37

**Table 9:** Presence or absence of lesions on chest CT and X-ray.................................................................38

**Table 10:** Comparison of preoperative and postoperative outcome of the chest imaging .................39

**Table 11:** The true positive, true negative, false positive and false negative rates of chest CT.........40

**Table 12:** The true positive, true negative, false positive and false negative rates of chest X-ray...........41

**Table 13:** Diagnostic characteristics of chest CT and X-ray for diagnosing lung metastases following rectal cancer........................................................................................................................................42

**Table 14:** Results of cTNM and pTNM after stage grouping........................................................................43

**Table 15:** Results of cTNM, pTNM and ypTNM displayed specifically for the patients diagnosed with lung metastases........................................................................................................................................44
1. Abstract

**Introduction:**
Until now, there is still no consensus whether routine use of preoperative imaging of the chest with CT and/or X-ray is recommended in staging patients with (colo-)rectal cancer to detect early lung metastases. The stage of cancer often determines the prognosis and the therapy approach of the patient. Over the past years an increasing number of articles were written about this subject, but still there are no general guidelines existing. The benefits of using preoperative imaging should be weighed against the adverse effects of it. Only a small percentage of the patients with colorectal cancer develop lung metastases during the course of disease and due to the low specificity of chest CT there is a greater chance of getting false positive results.

**Aim of this study:**
The aim of this study was to evaluate the clinical value of routine imaging of the chest preoperatively with CT and/or X-ray, for staging rectal cancer.
Another purpose was to compare the incidence of lung metastases following rectal cancer, obtained in this research, to the incidence of lung metastases following colon cancer, obtained from literature regarding this subject.

**Materials and methods:**
In this retrospective study, patients with rectal cancer were selected over a period from 21/06/2005 until 26/05/2011 on the Department of the Gastrointestinal Surgery at the Ghent University Hospital. Among other things, following data were collected: cTNM, (y)pTNM, preoperative and postoperative chest CT and chest X-ray. The patients included were selected on the basis of certain criteria and the total number of patients used in this study was 118. The obtained data were statistically processed and interpreted afterwards. Also articles relevant to this subject were searched with the databases Pubmed and Web of Science.
**Results:**
Of the 118 patients with rectal cancer, eventually 11.02% developed lung metastases of which approximately half were synchronous metastases and the other half were metachronous. This is in line with the higher incidence of lung metastases in rectal cancer when compared to the incidence of lung metastases following colon cancer, obtained from literature regarding this subject. 23.96% of the patients were diagnosed with indeterminate lung lesions. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of chest CT were respectively: 81.82%; 56.48%; 19.57%; 96.00%; 59.38%. For chest X-ray this was respectively: 27.27%; 97.75%; 60.00%; 91.58%; 90.00%. The survival rate was the lowest in cTNM group stage IV (59.1%) and pTNM group stage III (55.0%). The 5-year survival rate in the group of patients with lung metastases was 53.8%. The detection rate of lung metastases with chest X-ray was 3.00%. The two largest groups of patients with the highest number of lung metastases consisted of patients staged at cT3 and cT4. 5.09% of the total population would not have been diagnosed with lung metastases if only a chest X-ray and no chest CT was performed.

**Conclusion:**
Because of the low detection rate of lung metastases in patients with rectal cancer, the routine use of preoperative chest X-ray is not recommended. Also the routine use of preoperative chest CT is not recommended because of the low prevalence of lung metastases in patients with rectal cancer, the higher risk of false positive results when using chest CT and the potential harmful effects associated with imaging. Still, patients with high risk on developing lung metastases (cT3 and cT4) should always receive a preoperative chest CT to detect lung lesions, so that the patients can be followed more closely in the future. It remains of great importance that more research is done to further define patients with rectal cancer who have a higher risk of developing lung metastases. This research also confirmed a higher incidence of lung metastases in patients diagnosed with rectal cancer than in patients diagnosed with colon cancer.
1. Abstract

Inleiding:
Tot op heden is er nog steeds geen consensus over het routinematig gebruik van pre-operatieve CT en/of RX thorax bij patiënten met (colo-)rectale kanker om vroegtijdig longmetastasen op te sporen. Het stadium waarin de patiënt zich bevindt, bepaalt meestal de prognose en de therapeutische benadering van deze patiënt. In de afgelopen jaren zijn er steeds meer artikels gepubliceerd over dit onderwerp, maar nog steeds zijn er geen algemene richtlijnen voorhanden. De voordelen van pre-operatieve beeldvorming moet worden afgewogen tegenover de nadelige effecten ervan. Slechts een klein percentage van de patiënten met colorectale kanker ontwikkelt uiteindelijk longmetastasen. Bovendien is er een grotere kans op vals-positieve resultaten door de lage specificiteit van CT thorax.

Doel van dit onderzoek:
Het doel van deze studie was het bepalen van de klinische waarde van het routinematig gebruik van pre-operatieve beeldvorming van de thorax met CT en/of RX bij patiënten met rectumkanker. Een andere opzet was de incidentie van longmetastasen bij de patiënten met rectumkanker te onderzoeken en deze resultaten te vergelijken met de incidentie van longmetastasen bij patiënten met colonkanker, welke verkregen is uit literatuur over dit onderwerp.

Materialen en methode:
In deze retrospectieve studie werden patiënten met rectumkanker geselecteerd over een periode van 21/06/2005 tot 26/05/2011 op de afdeling van Gastro-Intestinale Chirurgie aan het Universitair Ziekenhuis van Gent. Onder andere werden de volgende gegevens verzameld: cTNM, (y)pTNM, pre- en post-operatieve CT thorax en RX thorax. De patiënten werden geselecteerd op basis van diverse criteria en het totaal aantal patiënten in deze studie was 118. De verkregen gegevens werden statistisch verwerkt en geinterpreteerd. Ook artikelen die relevant waren met betrekking tot deze studie werden gezocht via de databases Pubmed en Web of Science.
Resultaten:
Van de 118 patiënten met rectumkanker, ontwikkelden uiteindelijk 11,02% longmetastasen, waarvan ongeveer de helft synchrone en de andere helft metachrone metastasen waren. Dit is in lijn met de hogere incidentie van longmetastasen in rectumkanker, vergeleken met de incidentie van longmetastasen in colonkanker. 23,96% van de patiënten werd gediagnosticeerd met indeterminate lung lesions. De sensitiviteit, specificiteit, positief voorspellende waarde, negatief voorspellende waarde en de accuraatheid van CT thorax waren respectievelijk: 81,82%, 56,48%, 19,57%, 96,00%, 59,38%. Voor RX thorax waren deze respectievelijk 27,27%, 97,75%, 60,00%, 91,58%, 90,00%. Het overlevingspercentage was het laagst in cTNM stadium IV (59,1%) en pTNM stadium III (55,0%). De 5-jaarsoverleving in de groep van patiënten met longmetastasen was 53,8%. Het percentage longmetastasen ontdekt met RX thorax was 3,00%. De twee grootste groepen patiënten met het hoogste aantal longmetastasen waren deze in stadium cT3 and cT4. 5,09% van alle patiënten zou niet met longmetastasen gediagnosticeerd zijn, indien enkel een RX thorax en geen CT thorax zou zijn uitgevoerd.

Conclusie:
Vanwege het laag percentage longmetastasen dat wordt ontdekt met RX thorax bij patiënten met rectumkanker, is het routinematig gebruik van pre-operatieve RX van de thorax niet aanbevolen. Ook het routinematig gebruik van pre-operatieve CT thorax wordt niet aanbevolen omwille van de lage prevalentie van longmetastasen bij patiënten met rectumkanker, het hogere risico op vals-positieve resultaten bij het gebruik van CT thorax en de mogelijke schadelijke effecten geassocieerd met beeldvorming. Toch zouden patiënten met een hoog risico op het ontwikkelen van longmetastasen (cT3 and cT4) altijd een pre-operatieve CT thorax moeten krijgen om eventuele longlesies te detecteren, opdat de patiënten beter zouden opgevolgd kunnen worden in de toekomst. Desalniettemin blijft het van groot belang dat er nog meer onderzoek wordt uitgevoerd om patiënten met rectumkanker met een hoger risico op het ontwikkelen van longmetastasen te kunnen definiëren.
Dit onderzoek bevestigde verder ook de hogere incidentie van longmetastasen bij patiënten met rectumkanker dan bij patiënten met colonkanker.
2. Introduction

2.1. General introduction

Preoperative staging of patients with colorectal cancer often changes their prognosis and choice of therapy (1, 3-5). It is also very useful to evaluate the effects of therapy (3, 6). Synchronous and metachronous metastases in colorectal cancer are usually detected in the liver and in the lung (1, 7). About 19% to 30% of the patients have synchronous metastases when colorectal cancer is diagnosed (1, 2, 8). 20% to 50% will have metachronous metastases at some point after surgery (8). By all means, approximately 5-10% of the patients with colorectal cancer will develop lung metastases at some point during or after the actual diagnosis took place (7-10). The exact frequency of synchronous and metachronous lung metastases is not known (2). The reported incidence of synchronous lung metastases of colorectal cancer varies largely, from 3% to 18%. This could be due to the lack of obtainable histological proof of lung metastases (1).

2.1.1. Influence of metastases on survival

Detection of potentially resectable metastases has the greatest impact on survival (9). The main cause of deaths from cancer are distant metastases (8, 11). The liver is the most common site of metastatic disease. This implies that preoperative abdominal imaging should have the greatest impact on the initial approach. About 15% of the patients with liver metastases, will have resectable disease, with a 5-year survival rate following resection ranging from 30% to 40 % (3). However, the lung represents the most common site of extra abdominal disease and lung metastases represent the largest proportion of resectable distant disease, with a 5-year survival rate following resection ranging from 30% to 60% (2-4). If the metastasis is detected early, the possibility of curative resection will be higher (9). The overall survival of patients with metastatic disease has improved a lot over the last 20 years. This is partly attributed to the use of combination of chemotherapeutic regimens. Today the median overall survival may reach 2-3 years using systemic therapy. Still, a greater attribution to the increasing overall survival of patients is the result of the extension of surgery to metastatic disease (8).

(*) Synchronous lung metastasis: when diagnosed within three months following the diagnosis of rectal cancer
Metachronous lung metastasis: when diagnosed at least three months after the diagnosis of rectal cancer (2).
2.1.2. Sensitivity and specificity of chest CT and chest X-ray

Chest CT imaging in particular, is now the most sensitive technique available to detect lung metastases (1, 2, 8, 12), with a sensitivity over 70% and almost doubling the sensitivity of chest X-ray (8). Nevertheless it appears to be less specific than chest X-ray and thus not all abnormal lesions detected will be metastatic (8, 9). Chest CT detects lesions of 2-3 mm in size, whereas chest X-ray detects only 5-10 mm lesions (9). But yet, the difficulty remains to identify the nature of the smaller lesions on chest CT, due to the low specificity (8). Chest X-ray has a low detection rate of lung metastases and a small influence on patient management. The evidence to support the use of X-ray is scarce (4).

2.1.3. Guidelines for the use of preoperative imaging by chest CT and/or X-ray

Until now, guidelines for the use of preoperative imaging by chest CT and/or X-ray for staging rectal cancer are not very clear and there is a wide variation in the routine clinical practice (3, 4). This is particularly due to lack of clear instructions from published guidelines and authoritative bodies (3), but also to the frequent findings of indeterminate lesions (*) on chest CT (20-30%) (1). 10%-20% of these indeterminate lesions indeed seem to be lung metastases afterwards (8, 13). The most common current guidelines of different oncological societies regarding the preoperative imaging of the chest with CT and/or X-ray in patients with rectal cancer were compared (Table 1).

(*) Indeterminate lesions are defined as lesions seen on chest CT that could not be judged by the radiologist as either benign or malignant (1).
Table 1: Comparison of the most common current guidelines regarding the preoperative imaging of the chest with CT and/or X-ray in staging patients with rectal cancer

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Guidelines for preoperative imaging of the chest with CT and/or X-ray in patients with rectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO (14)</td>
<td>Always perform a preoperative chest X-ray (alternatively a chest CT scan can be carried out)</td>
</tr>
<tr>
<td>Oncological Manual of Ghent University Hospital (15)</td>
<td>Always perform a preoperative chest CT scan</td>
</tr>
<tr>
<td>NCI (16)</td>
<td>Always perform a preoperative chest CT scan</td>
</tr>
<tr>
<td>ACPGB (17)</td>
<td>Always perform a preoperative chest CT scan</td>
</tr>
<tr>
<td>NICE (18)</td>
<td>Always perform a preoperative chest CT scan</td>
</tr>
</tbody>
</table>

2.1.4. Difference in incidence of lung metastases between colon and rectal cancer

Some sources claim a higher incidence of metastases in the lung when having rectal cancer, in comparison to having colon cancer, where they suggest a lower incidence of metastases (1, 2, 11, 19, 20). This could be explained by the different routes of venous drainage (9, 11). The venous drainage of the colon is via the portal system, therefore the first site of hematogenous spread of tumors from the colon has always been regarded as the liver. And yet metastases bypassing the liver have been mentioned in several articles over the years, including spreading to the lung (11). The higher incidence of isolated lung metastases in rectal cancer, was attributed to the direct hematogenous spread into the systemic circulation via the inferior and middle rectal veins, bypassing the portal venous system. The results regarding the incidence of lung metastases in colon and/or rectal cancer per article taken into account for this study were summarized (Table 2) (1, 2, 11, 19, 20).
Table 2: Incidence of lung metastases in colon and/or rectal cancer per article

<table>
<thead>
<tr>
<th>Article</th>
<th>Number of patients in the respective articles with colon and/or rectal cancer</th>
<th>Incidence of lung metastases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grossman et al. (1) *</td>
<td>Colon (129 patients)</td>
<td>4.65</td>
</tr>
<tr>
<td></td>
<td>Rectum (71 patients)</td>
<td>9.86</td>
</tr>
<tr>
<td>Mitry et al. (2) *</td>
<td>Colon (1105 patients)</td>
<td>9.40</td>
</tr>
<tr>
<td></td>
<td>Rectum (215 patients)</td>
<td>16.70</td>
</tr>
<tr>
<td>Tan et al. (11) **</td>
<td>Colon (558 patients)</td>
<td>5.91</td>
</tr>
<tr>
<td></td>
<td>Rectum (196 patients)</td>
<td>11.74</td>
</tr>
<tr>
<td>Pihl et al. (19) **</td>
<td>Colon (565 patients)</td>
<td>3.50</td>
</tr>
<tr>
<td></td>
<td>Rectum (1013 patients)</td>
<td>11.50</td>
</tr>
<tr>
<td>Kirke et al. (20) *</td>
<td>Colon</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td>Rectum (56 patients)</td>
<td>17.86</td>
</tr>
<tr>
<td>Present study **</td>
<td>Colon</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td>Rectum (118 patients)</td>
<td>11.02</td>
</tr>
</tbody>
</table>

* Incidence of synchronous lung metastases
** Incidence of synchronous and metachronous lung metastases

2.1.5. Purpose of this study

The aim of this study was to evaluate the clinical value of routine imaging of the chest preoperatively with CT and/or X-ray, in staging rectal cancer. Another purpose was to compare the incidence of lung metastases following rectal cancer, obtained in this research, to the incidence of lung metastases following colon cancer, obtained from literature regarding this subject.

2.2. Types of colorectal cancer

Most colorectal cancers are adenocarcinomas (cancer of the epithelial cells, specifically in the glands, that line the inside tissue of the colon and rectum). Other types of cancer that can occur in the colon and/or rectum are following: carcinoid tumor, gastrointestinal stromal tumor (GIST) and lymphoma. These types of cancer are rather rare (21).
2.3. **Epidemiology of colorectal cancer**

2.3.1. **Epidemiology of colorectal cancer: Belgium**

Nowadays, in Belgium, colorectal cancer is the third most common diagnosed cancer within the male population. Prostate cancer and lung cancer are respectively the first and second most diagnosed cancer. In the female population, the most common cancers are respectively breast cancer, colorectal cancer and lung cancer (22, 23).

Colorectal cancer is seen more frequently in the male population (mean age: 69 year) than in the female population (mean age: 72 year). It is seldomly seen in people younger than 40 years old, but the number of colorectal cancers increases quickly after the age of 50. More than half of these cancers are located in the distal region of the bowel (rectum and sigmoid) (23).

In 2004, 4113 men and 3514 women in Belgium were diagnosed with colorectal cancer. In the year 2007, this was respectively 4251 and 3645 (22). The number of new cases of colorectal cancer in the different regions of Belgium in 2004 and 2007 were displayed (Tables 3 and 4).

**Table 3**: Number of new cases of colorectal cancer in Belgium in the year 2004 (22)

<table>
<thead>
<tr>
<th>Region</th>
<th>Belgium</th>
<th>Flanders</th>
<th>Wallonia</th>
<th>Brussels Capital Region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>7</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>25</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>35</td>
<td>23</td>
<td>20</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>40</td>
<td>65</td>
<td>49</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td>45</td>
<td>131</td>
<td>79</td>
<td>79</td>
<td>47</td>
</tr>
<tr>
<td>50</td>
<td>174</td>
<td>148</td>
<td>102</td>
<td>95</td>
</tr>
<tr>
<td>55</td>
<td>340</td>
<td>247</td>
<td>192</td>
<td>150</td>
</tr>
<tr>
<td>60</td>
<td>414</td>
<td>279</td>
<td>267</td>
<td>161</td>
</tr>
<tr>
<td>65</td>
<td>664</td>
<td>384</td>
<td>433</td>
<td>234</td>
</tr>
<tr>
<td>70</td>
<td>768</td>
<td>577</td>
<td>502</td>
<td>338</td>
</tr>
<tr>
<td>75</td>
<td>741</td>
<td>636</td>
<td>480</td>
<td>380</td>
</tr>
<tr>
<td>80</td>
<td>530</td>
<td>636</td>
<td>343</td>
<td>358</td>
</tr>
<tr>
<td>85</td>
<td>239</td>
<td>429</td>
<td>152</td>
<td>238</td>
</tr>
<tr>
<td>Total</td>
<td>4113</td>
<td>3514</td>
<td>2617</td>
<td>2055</td>
</tr>
</tbody>
</table>
Table 4: Number of new cases of colorectal cancer in Belgium in the year 2007 (22)

<table>
<thead>
<tr>
<th>Region</th>
<th>Belgium</th>
<th>Flanders</th>
<th>Wallonia</th>
<th>Brussels Capital Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
<td>10</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>25</td>
<td>6</td>
<td>10</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>30</td>
<td>22</td>
<td>12</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>35</td>
<td>25</td>
<td>26</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>40</td>
<td>57</td>
<td>66</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>45</td>
<td>124</td>
<td>97</td>
<td>76</td>
<td>56</td>
</tr>
<tr>
<td>50</td>
<td>206</td>
<td>168</td>
<td>116</td>
<td>106</td>
</tr>
<tr>
<td>55</td>
<td>363</td>
<td>252</td>
<td>236</td>
<td>136</td>
</tr>
<tr>
<td>60</td>
<td>494</td>
<td>302</td>
<td>303</td>
<td>182</td>
</tr>
<tr>
<td>65</td>
<td>523</td>
<td>386</td>
<td>347</td>
<td>260</td>
</tr>
<tr>
<td>70</td>
<td>741</td>
<td>487</td>
<td>480</td>
<td>306</td>
</tr>
<tr>
<td>75</td>
<td>782</td>
<td>661</td>
<td>514</td>
<td>385</td>
</tr>
<tr>
<td>80</td>
<td>602</td>
<td>643</td>
<td>368</td>
<td>389</td>
</tr>
<tr>
<td>85</td>
<td>298</td>
<td>514</td>
<td>187</td>
<td>316</td>
</tr>
<tr>
<td>Total</td>
<td>4251</td>
<td>3645</td>
<td>2695</td>
<td>2219</td>
</tr>
</tbody>
</table>

The trends that exist in the incidence of colorectal cancer from the year 2004 up to 2007 in the male and female population in the different regions of Belgium were displayed (Figure 1). In the year 2007, the lowest incidence is seen in the female population of Brussels, whereas the highest incidence is seen in the male population of Flanders. In general, the incidence of colorectal cancer has increased in the year 2007, except for the male population of Brussels and the female population of Wallonia.

Fig. 1: Trends in incidence of colorectal cancer in Belgium (22)
2.3.2. Epidemiology of colorectal cancer: global

Colorectal cancer is the third most common cancer in the world. Lung cancer and breast cancer are respectively the first and second most common diagnosed cancer (Figure 2). An estimated 1.24 million people worldwide were diagnosed with colorectal cancer in 2008 (10% of the total amount of cancers worldwide) (24). Europe has the highest incidence of colorectal cancer, followed by North and South America. Africa has the lowest incidence. Colorectal cancer is more common in richer countries, but its incidence is rising in some developing nations (25).

![Graph showing the 20 most common diagnosed cancers worldwide, 2008 estimate (24)](image)

**Fig. 2:** The 20 most common diagnosed cancers worldwide, 2008 estimate (24)

The incidence of colorectal cancer worldwide is higher in men than in women (Male:Female ratio = 1.4 : 1.0). In both sexes, there is a difference regarding the incidence between the different regions of the world (24) (Figures 3 and 4).
Fig. 3: Incidence and mortality rates in the regions of the world, 2008 estimates (female) (24)

Fig. 4: Incidence and mortality rates in the regions of the world, 2008 estimates (male) (24)
2.4. **Symptoms of colorectal cancer**

Colorectal cancer can present symptoms in many different ways that are not always typical. The kind of symptoms and the rapidity of progression depend on the localization of the tumor in the large bowel. Tumors that are localized at the distal end of the bowel can cause red blood loss per anum, traces of blood in the feces or on the toilet paper (23).

**Other symptoms (23):**

- Constipation
- Diarrhea
- Urge
- Anemia (following chronic blood loss at the level of the lesion) and thus fatigue
- Inexplicable weight loss
- Abdominal pains (often in the form of irregular cramps)

None of these symptoms automatically indicate colorectal cancer, but should be a reason for further investigation of the patient (23)!

2.5. **Risk factors for colorectal cancer**

Most colorectal cancers are the result of numerous interactions between (still unknown) carcinogens and genetic factors (23).

**Following factors (probably) play an important role in the development of colorectal cancer:**

- **Age:** more than 90% of the colorectal cancers occur in people over the age of 50 (21).
- **Nutrition** (carcinogens, chemical substances, protective substances, ...): some studies have shown that colorectal cancer occurs more often when people eat food that contains more animal fats than fibres (23).
- **Lack of physical activity:** due to reduced blood flow in the bowel wall (23).
- **Constipation:** which results in an increased contact time between the bowel wall and the carcinogens in the feces (23).
- **Smoking** (?): some studies show a higher incidence of colorectal cancer with patients who smoke. This is probably due to the transport of carcinogens to the colon from inhaled or swallowed tobacco smoke (25).
There are also other risk factors that play an important role (23):

- **Presence of adenomas** (start as benign polyps) on the mucosa of the bowel wall. The larger the adenoma, the larger the malignancy potential.

- **Inflammatory bowel disease (IBD)**: patients diagnosed with ulcerative colitis have a higher risk to develop colorectal cancer than patients diagnosed with Crohn’s disease.

- A patient with a **history of a first case of colorectal cancer** has a greater risk to develop colorectal cancer a second time, unrelated to the first case.

- **Heredity** (there is a three times higher risk for first degree relatives)
  - Hereditary Nonpolyposis Colon Cancer (HNPCC) or Lynch Syndrome (26)
    - *Autosomal dominant inheritance*
    This is the most common of the known hereditary colon cancer syndromes and occurs approximately at the age of 40. Although, recent data indicate that the median age of colon cancer diagnosis may be as high as 61 years (27). The cancer commonly presents with only a few adenomas that rapidly progress to malignancy compared to adenomas occurring in the general population. Also extracolonic malignancies manifest in Lynch Syndrome (e.g.: endometrial, gastric, ovarian, urinary collecting system, …)
  - Familial Adenomatous Polyposis (FAP) (26)
    - *Autosomal dominant inheritance*
    This is the most common polyposis syndrome and occurs characteristically in the second decade of life. Colorectal cancer develops in patients with FAP at the age of 40 or 10-15 years after the initial development of polyposis. It is a typically progressive disease, with the development of hundreds to thousands of adenomatous polyps in the colon and rectum. There is 100% penetrance among the affected individuals.

**Following factors might lower a person’s risk on developing colorectal cancer (21):**

- **Non Steroidal Anti-Inflammatory Drugs (NSAIDs)**: some studies suggest that NSAIDs reduce the development of polyps in people with a history of polyps and/or colorectal cancer. Nevertheless, the use of NSAID is strongly associated with major side effects, e.g. bleeding of the stomach.

- **Diet and supplements**: a diet low in red meat and rich in vegetables and fruits may reduce the risk on developing colorectal cancer. Some studies also claim that people who take calcium and vitamin D supplements have a lower risk of colorectal cancer.
3. Materials \& methods

3.1. Literature study

Articles were found by using exclusion- and inclusion criteria. Pubmed and Web of Science are the two databases that were used, with the following terms: [\text{col* OR rect* AND staging AND (cancer OR carcinoma OR adenocarcinoma) AND (chest OR thorax) AND (imaging OR CT OR radio* OR Xray OR tomography)}] \textbf{(Figure 5)}. One article [Thompson and Halvorsen 1987] was found by searching the database of Google Scholar. It did appear to be present in Pubmed, but was initially not found by using the terms used above.

Another purpose of this research was to see if there is a proof of a higher incidence of metastases in the lung when having rectal cancer, in comparison to having colon cancer, where a few sources suggest a lower incidence of metastases (1, 2, 11, 19, 20). The keywords used for this search were: [\text{col* OR rect* AND (cancer OR carcinoma OR adenocarcinoma) AND (chest OR lung) AND metastases AND (incidence OR pattern OR distribution)}] \textbf{(Figure 6)}. Clearly, there were more articles found, but there were less relevant articles when compared to the previous search.

As the study progressed, more relevant information had to be searched. Also new articles regarding this subject were published. These were used in this research as well.
**Fig. 5:** Flowchart of selection of articles about the use of preoperative imaging of the chest regarding the staging of (colo-)rectal cancer.

**Terms used:** (colo* OR rect*) AND staging AND (cancer OR carcinoma or adenocarcinoma) AND (chest OR lung) AND (imaging OR CT OR radio* OR X-ray OR tomography)

**Databases used and the corresponding number of articles:**
- Pubmed: 27 articles, including 4 review articles and 1 article found via Google Scholar
- Web of Science: 48 articles, including 5 review articles

**Exclusion criteria:**
- Title & abstract
- ‘full text’
- Language (Norwegian article)
- Metastases found somewhere else in the body than in the lungs
- Subject irrelevant
- Other imaging techniques
- Article already found in Pubmed or Web of Science (13 mutual articles)

**Selection:**
- Pubmed: 9 articles, including 1 review article
- Web of Science: 6 articles
- Articles found through references from articles that have already been read: 2
**Fig. 6:** Flowchart of selection of articles about the evidence of higher incidence of lung metastases occurring in rectal cancer in comparison to colon cancer

Terms used: (colo* OR rect*) AND (cancer OR carcinoma or adenocarcinoma) AND (chest OR lung) AND metastases AND (incidence OR pattern OR distribution)

Databases used and corresponding number of articles:
- Pubmed: 255 articles, including 28 review articles
- Web of Science: 303 articles, including 20 review articles

Exclusion criteria:
- Title & abstract
- ‘full text'
- Metastases found somewhere else in the body than in the lungs
- Subject irrelevant
- Article already found in Pubmed or Web of Science (23 mutual articles)

Selection:
Pubmed: 1 review article
Web of Science: 2 articles

**3.1.1. Current guidelines regarding management of rectal cancer**

In Belgium, PROCARE (PROject on CAncer of the REctum) is a multidisciplinary driven project by all members of the Belgian Section for Colorectal Surgery. Guidelines on the management of rectal cancer were discussed and upgraded with recently published evidence (28). The guidelines described in this study were mostly based on the PROCARE Guidelines (29).
3.1.1.1. **Preoperative guidelines regarding rectal cancer**

The difference between rectal and colon cancer is based on the distal distance of the tumor with respect to the margo ani. With a rigid proctoscopy this can be verified. When the tumor is located 15 cm or less from the margo ani, it is defined as rectal cancer (29).

- **Use of colonoscopy**
  After rectal cancer has been diagnosed, it is recommended to perform a total colonoscopy with resection of any polyps when detected during the investigation. In case a total colonoscopy is refused by the patient or when it is too risky or impossible to perform one (e.g. obstructive or perforated rectal cancer), a double-contrast barium enema of colon and rectum should be performed instead (29).

- **Use of the marker carcinoembryonic antigen (CEA)**
  The level of the tumor marker carcinoembryonic antigen (CEA) should also be tested in the blood of all patients diagnosed with rectal cancer before any operation takes place (29). CEA is a complex glycoprotein that is pathologically elevated in certain malignancies, particularly cancers of the gastrointestinal tract (3). The low sensitivity and low specificity of this marker make it unuseful to screen and detect colorectal cancer itself. For example, the serum level of CEA can also be elevated in benign lesions (30) or in patients who smoke (3). Elevated levels of CEA in the blood are associated with poorer prognosis: preoperative serum CEA levels > 5.0 µg/l have an adverse impact on survival that is independent of tumor stage (3). Elevated CEA levels could also indicate the presence of metastases (30). Lung metastases are less associated with an elevated CEA than liver metastases (29). Measuring CEA levels is also very useful to evaluate therapy and to detect recurrence of the tumor (30): if an elevated preoperative level does not normalize after surgery, this could imply residual or recurrent disease (3). The use of other tumor markers is not proven to be very useful because of lack of evidence. Also routine blood tests or molecular markers have no prognostic or predictive value (29).

- **Use of CT scan**
  To detect metastases in patients with rectal cancer, preoperative imaging with CT of the chest and abdomen/pelvis is indicated (29).
- **Use of Transrectal Ultrasonography (TRUS)**
  TRUS is indicated when the patient is diagnosed with a non-stenosing rectal tumor that is resectable and localized in the mid-third and lower-third of the rectum (29).

- **Use of NMR**
  High resolution NMR is used to confirm uT3/4 and uN+ tumors, tumors located in the upper third of the rectum and it is also used to determine the tumor-free lateral margin (29).

- **Use of 18 Fluoro – 2 Deoxy – D Glucose – Positron Emission Tomography (FDG-PET)**
  This can be useful to detect recurrent disease, but routine use is not recommended at the time of initial diagnosis, because it practically does not alter the treatment approach (31).

A summary explaining the preoperative guidelines was displayed (Figure 7).

**Fig. 7: Diagnosis and staging of rectal cancer (29)**

- Palpatio per anum
- Proctoscopy
- Rectal tumor biopsy

```
- Palpatio per anum
- Proctoscopy
- Rectal tumor biopsy

Total colonoscopy

CEA

Spiral CT of chest and abdomen/pelvis to detect metastases

TRUS when non-stenosing rectal tumor ≤ 10 cm

High Resolution NMR:
- Stenosing tumors
- Tumors < 10 cm
- Tumors ≥ uT3 or uN+
```
3.1.1.2. Staging of rectal cancer (TNM classification)

Nowadays, the most common way to stage rectal cancer is by using the TNM classification (20, 32). As mentioned in the introduction, staging of tumors plays a fundamental role in the treatment of patients and is also a very powerful and reliable predictor of prognosis. It represents the operational basis for choosing the most appropriate therapy (32). One of the strengths of the current TNM staging is the possibility of uniform use, thanks to the rules of application. Still, there is an emerging need to further stratify patients with the same tumor stage, for planning most appropriate treatments. This expansion comes with a risk that optional or additional terms could avoid uniform use (32).

**Structure of TNM-classification:**

The structure of TNM classification is mainly quantitative: it is based on anatomic descriptors (pT1-pT4: according to the involved layers of the intestinal wall, pN1-pN2: according to the number of metastatic lymph nodes, pM1: occurrence of distant metastasis) (32). However, a qualitative structure should also be applied (e.g. aggressiveness and information on how to prevent progression), to better estimate prognosis and plan treatment. This could avoid the potential risk of considering the TNM classification as insufficient for clinical use (32).

**Advantages of the TNM classification:**

Although it practically only relies on the assessment of the anatomic extent of the disease at the time of diagnosis, the TNM classification still has a lot of advantages when compared to the former used staging system: the Dukes’ classification system (32).

The TNM classification (32):

- delivers a full stratification of the bowel wall involvement and the peritoneal serosa.
- also takes into account the number of regional lymph node metastases.
- has a ‘multidisciplinary design’:
  - Clinical (pretreatment) classification: cTNM
  - Pathologic (postsurgical) classification: pTNM
  - After preoperative chemoradiotherapy: ypTNM
- is a ‘dynamic’ staging system: it has been continuously updated through an ongoing expert review of all the available data, resulting in the existence of several editions.
Staging of rectal cancer must be done following certain procedures according to the TNM classification:

In the latest edition of the TNM Classification (7th edition), the basic categories are unchanged compared to the 6th edition. However, the subdivisions did get expanded. Below, these changes are displayed in italic. The tumors of the rectum have undergone few changes between the TNM-6 and the TNM-7 (33).

- **T (tumor)** (34):
  - Physical examination
  - Imaging
  - Endoscopic US and/or surgical exploration
  - NMR

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ: intraepithelial or invasion of lamina propria

T1: Tumor invades submucosa

T2: Tumor invades muscularis propria

T3: Tumor invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues

T4: Tumor directly invades other organs or structures and/or perforates visceral peritoneum

  - **T4a: Tumor perforates visceral peritoneum**
  - **T4b: Tumor directly invades other organs or structures**

- **N (node)** (34):
  - Physical examination
  - Imaging
  - And/or surgical exploration

Nx: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis in 1 – 3 regional lymph nodes

  - **N1a: Metastasis in 1 node**
  - **N1b: Metastasis in 2-3 nodes**
  - **N1c: Satellites in subserosa, without regional lymph nodes**

N2: Metastasis in ≥ 4 regional lymph nodes

  - **N2a: Metastasis in 4-6 lymph nodes**
  - **N2b: Metastasis in ≥ 7 lymph nodes**
Metastasis in nodes of the rectum other than the following, is classified as distant metastasis:
superior, middle, inferior rectal (haemorrhoidal), inferior mesenteric, internal iliac, mesorectal
(paraproctal), lateral sacral, presacral, sacral promonontory (Gerota).

- **M (metastasis)** (34):
  - Physical examination
  - Imaging
  - Endoscopy and/or surgical exploration

Mx: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis
  - **M1a**: 1 organ
  - **M1b**: > 1 organ or peritoneum

**Stage Grouping** (34):

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>T1, T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T1, T2</td>
<td>N1 (≤ 3 lnn)</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA III</td>
<td>T1</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I IB III</td>
<td>T3, T4a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III A</td>
<td>T2, T3</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III A</td>
<td>T1, T2</td>
<td>N2b</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III A</td>
<td>T4a</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III A</td>
<td>T3, T4a</td>
<td>N2b</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III A</td>
<td>T4b</td>
<td>N1, N2 (&gt; 3 lnn)</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a</td>
</tr>
<tr>
<td>Stage I VB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
</tr>
</tbody>
</table>
• **G (grade)** (21):
  Describes in which extent the tumor has the aspect of normal tissue. The grade can help to predict how quickly the cancer may grow (well differentiated vs. poorly differentiated or undifferentiated). A lower grade means a better prognosis.
  
  Gx: Tumor grade cannot be assessed
  G1: Cells are well differentiated
  G2: Cells are moderately differentiated
  G3: Cells are poorly differentiated
  G4: Cells are undifferentiated

3.1.1.3. **Therapeutic guidelines regarding rectal cancer**

As already mentioned, the prognosis of rectal cancer depends on the TNM classification (degree of penetration of the tumor through the bowel wall, presence or absence of lymph node involvement and/or metastases) (20). Not only the prognosis, but also the choice of management depends strongly on the staging of the tumor (15).

**Neoadjuvant therapy of rectal cancer** (29):

A **long-course preoperative chemoradiotherapy (CRT)** is recommended in every patient diagnosed with stage II or stage III rectal cancer. 25 x 1.8 Gy combined with 5 Fluorouracil (5-FU) based chemotherapy is administered. 6-8 weeks after CRT, surgery can be carried out: downstaging of the tumor improves tumor resectability.

A **short-course of preoperative radiotherapy (RT)** is recommended in patients with a low risk for local recurrence (rectal cancer situated in the middle or upper third of the rectum and/or with a circumferential margin (CRM) > 2 mm). Within a week after RT, surgery must be carried out.

A summary explaining the preoperative therapeutic guidelines was displayed (**Figure 8**).
Fig. 8: Neoadjuvant therapy guidelines regarding resectable rectal cancer (29)

- Lower third (0-5cm)
  - cStage I: radical excision (Transanal Endoscopic Microsurgery – TEMS or Local Excision – LE)
  - cStage II – III: 45 Gy CRT. 6-8 weeks after CRT: radical excision

- Middle & upper third (5.1-15cm)
  - cStage I: radical excision (TEMS or LE)
  - cStage II:
    - cT3 & CRM > 2:
      25 Gy RT. Within 1 week after RT: radical excision
    - cT4 or CRM < 2:
      45 Gy RCT. 6-8 weeks after CRT: radical excision
  - cStage III: 45 Gy RCT. 6-8 weeks after CRT: radical excision

Adjuvant therapy of rectal cancer (3 months after surgery) (29):
In patients diagnosed with stage II or stage III rectal cancer, who received preoperative RT without chemotherapy (CT), adjuvant chemotherapy with 5-FU may be considered during 4 or 6 months respectively in stage II and stage III rectal cancer patients.

In patients who did not receive neoadjuvant therapy, adjuvant CRT may be considered.

Until now, there is no evidence to administer adjuvant CT in stage III rectal cancer patients who were treated with neoadjuvant CRT.

A summary explaining the preoperative therapeutic guidelines was displayed (Figure 9).

Fig. 9: Adjuvant therapy guidelines regarding rectal cancer (29)

- cStage 0 – I
  - No neoadjuvant R/ or 25 Gy RT:
    - (y)pStage I:
      nothing
    - (y)pStage II – III:
      CRT if no preoperative
      25 Gy RT + 4-6 months CT

- cStage II & III
  - No neoadjuvant R/ or 25 Gy RT:
    - (y)pStage 0 – I:
      nothing
    - (y)pStage II – III:
      CRT if no preoperative
      25 Gy RT + 4-6 months CT

- cStage II & III
  - Neoadjuvant 45 Gy CRT:
    - yStage 0 – I:
      nothing
    - yStage II – III:
      4-6 months CT
Stage IV rectal cancer:

- **Operable tumors with resectable lung and/or liver metastases (= curative):**
  Perioperative CT is recommended (29) + resection of primary tumor and/or lung and liver metastases (32).

- **No resection of metastases is possible (= non curative):**
  o If the primary tumor is *symptomatic* (for example: obstruction, anemia): palliative resection or stent (32). If the patient received no RT, CRT may be considered in case of pelvic pain in locally recurrent or advanced rectal cancer (29).
  o If the primary tumors is *asymptomatic*: no resection
  o Treatment of metastases: palliative chemotherapy (3, 15, 29). This increases the survival of patients with inoperable metastatic disease (4).

**Local recurrence of rectal cancer:**
The treatment depends on the stage of the tumor. If possible: curative resection, if not: ditto primary tumor (15).

**3.1.1.4. Postoperative guidelines (follow-up) regarding rectal cancer**

Some trials show no advantage of follow-up in terms of survival. Meta-analyses indicate that follow-up can offer survival benefit regarding earlier detection of metastatic or recurrent disease. Recurrence will be detected earlier, so treatment is often curative. Primary tumors can be detected this way as well (29).
Standard follow-up for all patients should contain the following (29):

- **History and physical examination (including digital examination):** every three months during the first three years. From the fourth year: repeat history and physical examination every six months.

Follow-up is not only useful to evaluate the patients' status, but has also an important psychological benefit for the patient.

- **Laboratory testing (CEA):** is done together with history and physical examination.

- **Radiological testing**
  - **Abdominal ultrasound** (since most metastases occur in the liver): every six months in the first three years (not when abdominal CT is done). From the fourth year: annually.
  
  Disadvantages:
  * Less accurate than CT or NMR in diagnosing liver metastases.
  * Cannot assess recurrent pelvic disease following rectal cancer

  - **Chest X-ray:** every six months in the first three years (not when chest CT is done). From the fourth year: annually.

- **Total colonoscopy:** one year after surgery. If normal: repeat after three years. If still normal: colonoscopy every five years from then.

- There is no place for endoscopic ultrasound (EUS) in routine follow-up, but it remains a good tool for diagnosing local recurrence when suspected.

Stage II and stage III rectal cancer (at higher risk of local recurrent disease) (29):

Standard follow-up and:

- **Abdominal/pelvic CT** annually during the first three years.

  (There is no obvious difference between CT and NMR for detecting recurrence, although NMR is more useful due to a higher ability to differentiate scar tissue from recurrence (35)).

- **Abdominal ultrasound:** should be done between the CT scans.

- **Chest CT** annually during the first three years (thus: chest CT and X-ray will be done alternately at 6 months intervals during the first three years).
A summary explaining the postoperative guidelines was displayed (Figure 10).

**Fig. 10:** Postoperative guidelines regarding rectal cancer (29)

<table>
<thead>
<tr>
<th>cStage I and pStage I</th>
<th>cStage II and III and/or pStage II and III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1-3: /3 mo</td>
<td>Year 1-3: /3 mo</td>
</tr>
<tr>
<td>&gt; year 3: /6 mo</td>
<td>&gt; year 3: /6 mo</td>
</tr>
<tr>
<td>- Clinical examination</td>
<td>- Clinical examination</td>
</tr>
<tr>
<td>- CEA</td>
<td>- CEA</td>
</tr>
<tr>
<td>Year 1-3: /6 mo</td>
<td>Year 1-3: /year *</td>
</tr>
<tr>
<td>- Chest X-ray</td>
<td>&gt; year 3: /year</td>
</tr>
<tr>
<td>- Abdominal US</td>
<td>- Chest X-ray</td>
</tr>
<tr>
<td><strong>Year 1:</strong></td>
<td><strong>Year 1:</strong></td>
</tr>
<tr>
<td>- Colonoscopy</td>
<td>- Colonoscopy</td>
</tr>
<tr>
<td>→ If normal: repeat</td>
<td>→ If normal: repeat</td>
</tr>
<tr>
<td>after 3 years</td>
<td>after 3 years</td>
</tr>
<tr>
<td>→ if normal: repeat</td>
<td>→ if normal: repeat</td>
</tr>
<tr>
<td>every 5 years</td>
<td>every 5 years</td>
</tr>
<tr>
<td>* Chest CT and X-ray will be done alternately at 6 months intervals during the first three years. Ditto abdominal CT and US.</td>
<td></td>
</tr>
</tbody>
</table>

3.2. **Patient study**

3.2.1. **Definition and criteria**

This retrospective study was approved by the ethics committee of the Ghent University Hospital after submitting the document required for this approval. The patients included had rectal cancer and were selected over a period from 21/06/2005 until 26/05/2011 (six years’ term) on the Department of the Gastrointestinal Surgery at the Ghent University Hospital. The number of patients that were included at the beginning was 188. After working through this database, thirteen patients got excluded for different reasons (Figure 11).
Out of this group of 175 patients, 26 patients were reported deceased at that moment. The rest of the group (149 patients) was asked to fill in an informed consent form, whereof 92 had replied and agreed to participate in the study. These remaining patients were thus included in this study together with the deceased ones. Consequently, the total number of patients that were included at the end was 118. The gathered information was processed anonymously.
To attain the aim of this research, the following data of the patients were collected:

- Sex.
- Age.
- Tumor stage of the rectal cancer (cTNM and (y)pTNM).
- Date of operation.
- Data regarding preoperative and/or postoperative chest CT and/or X-ray and the fact if this imaging was pathological. When lesions were seen on the image at the time the imaging took place, they were described as ‘positive for lesions’. However, pleural fluid or strands, vascular lung lesions, fibrous lesions, emphysema and bullae were not taken into account (= negative for lesions).
- Number of patients who eventually got diagnosed with lung metastases (to determine the incidence and to see how many false positive and/or false negative diagnoses were made and how many diagnoses were actually true positive and/or true negative).
- Date of the imaging (to calculate the time interval between preoperative and/or postoperative chest CT/X-ray).
- Date of the last consultation or date of death in case the patient was already deceased (to realize a Kaplan-Meier curve in order to analyze the survival time).

Data processing:
The data obtained was entered into the spreadsheet application Microsoft Excel. Descriptive analysis was done with the program SPSS statistics 19. The data was described by using frequencies, measures of central tendency (means and medians) and measures of variability (standard deviation). To estimate the probability of survival of the population over time, the Kaplan Meier method was applied.
3.2.2. Description of how the data was collected

Data from the Electronic Patient Files (EPF):
More than half of the information regarding chest CT imaging (date of imaging and the presence or absence of lung metastases) were found in the EPF of these patients at the Department of the Gastrointestinal Surgery at the Ghent University Hospital. This was the case for 80 patients. However, not all the data could be obtained this way. In order to complete the database, several phone calls were made to each patients’ doctor. Just like the CT imaging, the information about chest X-ray, cTNM, (y)pTNM and the treatment with neoadjuvant chemotherapy, was obtained by searching the EPF of each of these patients.

Data from patients’ specialists and general practitioners:
Some of the patients in this study were referred to the Ghent University Hospital after being admitted in another hospital and others went to a different hospital after having the surgery in Ghent. Initially each of the treating specialists in these hospitals, were contacted to see if they had more information about the imaging. This was the case for 69 patients. More information from the remaining 26 patients was obtained by making contact with each of these patients’ general practitioner.

Data from the Pathological Anatomy Service at the University of Ghent:
In some cases, the tumor grade was not explicitly mentioned. In those cases, Prof. Dr. Wim Ceelen helped to compose them after looking into the anatomo-pathologic findings from the Pathological Anatomy Service at the University of Ghent. After collecting all the data about the TNM staging of the patients, each of these TNM stages were group staged, following the TNM Classification of Malignant Tumors, 6th edition (34).
4. Results

During the search for literature regarding the subject of this thesis, the first thing noticed, was the scarcity of articles with regard to the subject.

4.1. Population characteristics

4.1.1. Demographic data

40 of the 118 cases (33,90%) were female (F), whereas 66,10% were male (M) (M:F ratio = 1,95). The mean age of all patients was 63 (standard deviation: +/- 12,1).

4.1.2. Number and localization of metastases following rectal cancer

Of the 118 patients:

- 40 showed distant metastases (33,90%). 20 patients (16,95%) were diagnosed with synchronous metastases and the 20 other patients (16,95%) with metachronous metastases. Below, more details can also be found regarding number and localization of these metastases.
- 13 patients were diagnosed positive for lung metastases (11,02%).
- 8 patients had both liver- and lung metastases (6,78%).
- 4 patients showed a local recurrence of the rectal tumor (3,39%). One of these 4 patients had also liver metastases.
- 1 patient had a primary lung cancer (already present at the time the rectal tumor was diagnosed).
Number and localization of metastases following rectal cancer:

- Liver metastases: 22 (18.64%)
  - Including 13 synchronous metastases (11.02%)
  - Including 9 metachronous metastases (7.63%)
- Lung metastases: 13 (11.02%)
  - Including 6 synchronous metastases (5.09%)
  - Including 7 metachronous metastases (5.93%)
- Bone metastases: 2 (1.70%)
- Peritoneal metastases of the pelvis: 1 (0.85%)
- Mediastinal lymph nodes: 1 (0.85%)
- Adrenal medulla metastases: 1 (0.85%)
- Isolated local recurrence: 3 (2.54%)
- Local recurrence + liver metastases: 1 (0.85%)

A summary of these results was displayed (Figure 12).

**Fig. 12:** Summary of number and localization of metastases following rectal cancer

- **Total number of patients:** 118
4.1.3. **Survival analysis**

To estimate the probability of survival of the population over time, the Kaplan Meier method was applied.

- **Survival analysis of the total population on the basis of group staging of cTNM and pTNM**

First, the population was split into 2 groups: cTNM and pTNM. Afterwards, each of these groups was further divided into 4 groups, following group staging, namely: I, II, III and IV. These groups were analyzed through the Kaplan Meier method (*Figures 13 and 14*).

![Kaplan Meier Curve](image)

*Fig. 13: Survival analysis of the population (after group staging of cTNM) through a Kaplan Meier curve*
Fig. 14: Survival analysis of the population (after group staging of pTNM) through a Kaplan Meier curve

The 5-year survival rate of each group (i.e. the percentage that survived the stage over a period of 5 years) and the median survival time (i.e. the point at which 50% of the patients are still alive) were displayed (Tables 5 and 6)

**Table 5**: 5-year survival rate and median survival time of the total population per group stage of cTNM

<table>
<thead>
<tr>
<th>cTNM: Grouped staging</th>
<th>5-year survival rate (%)</th>
<th>Median survival time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>70,00</td>
<td>*</td>
</tr>
<tr>
<td>II</td>
<td>85,00</td>
<td>*</td>
</tr>
<tr>
<td>III</td>
<td>85,20</td>
<td>*</td>
</tr>
<tr>
<td>IV</td>
<td>59,10</td>
<td>27,80</td>
</tr>
<tr>
<td>Overall</td>
<td>77,60</td>
<td>*</td>
</tr>
</tbody>
</table>

* Median survival not reached
Table 6: 5-year survival rate and median survival time of the total population per group stage of pTNM

<table>
<thead>
<tr>
<th>pTNM: Grouped staging</th>
<th>5-year survival rate (%)</th>
<th>Median survival time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>81,80</td>
<td>*</td>
</tr>
<tr>
<td>II</td>
<td>94,70</td>
<td>*</td>
</tr>
<tr>
<td>III</td>
<td>55,00</td>
<td>46,20</td>
</tr>
<tr>
<td>IV</td>
<td>66,70</td>
<td>*</td>
</tr>
<tr>
<td>Overall</td>
<td>76,00</td>
<td>*</td>
</tr>
</tbody>
</table>

* Median survival not reached

- Survival analysis specifically of the patients diagnosed with lung metastases

The group of 13 patients diagnosed with lung metastases were analyzed through the Kaplan Meier method (Figure 15).

Fig. 15: Survival analysis of the group of patients diagnosed with lung metastases through a Kaplan Meier curve
The 5-year survival rate of the patients diagnosed with lung metastases and the median survival time were displayed (Table 7).

Table 7: 5-year survival rate and median survival time of the patients diagnosed with lung metastases

<table>
<thead>
<tr>
<th>Patients with lung metastases</th>
<th>5-year survival rate (%)</th>
<th>Median survival time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53,80</td>
<td>25,53</td>
</tr>
</tbody>
</table>

4.2 Chest CT and X-ray

4.2.1. Presence or absence of lung lesions on imaging of the chest

In total, 81,40% had a preoperative CT of the chest (96 patients), whereas 57,60% had a postoperative CT of the chest (68 patients). Out of the 118 patients, 60 had both preoperative and postoperative chest CT.

Of the 96 patients who had a preoperative CT scan
- Lung lesions were seen on imaging in 47,92% (46 of the 96)
- 10,42% (10 of the 96) were protocolled by the radiologist as having lung metastases.
- 23,96% (23 of the 96) were protocolled by the radiologist as having indeterminate lung lesions. 1 of these 23 patients eventually was diagnosed with lung metastases, which means that the remaining 22 patients were still diagnosed with indeterminate lesions (22,92%).
- 13,54% (13 of the 96) were protocolled by the radiologist as not having lung metastases, whilst lung lesions were seen on the chest CT scan.
Of the 68 patients who had a postoperative CT scan:

- Lung lesions were seen on imaging in 47.06% (32 of the 68).
- 11.77% (8 of the 68) were protocolled by the radiologist as having lung metastases.
- 7.35% (5 of the 68) were protocolled by the radiologist as having indeterminate lung lesions. 1 of these 5 patients eventually was diagnosed with lung metastases. Which means that the remaining 4 patients were still diagnosed with indeterminate Lesions (5.88%).
- 27.94% (19 of the 68) were protocolled by the radiologist as not having lung metastases, whilst lung lesions were seen on the chest CT scan.

These results were summarized (Table 8).

Table 8: Summary of the number of lung lesions protocolled by the radiologist as ‘lung metastases’, ‘indeterminate lung lesions’ and ‘no lung metastases’.

<table>
<thead>
<tr>
<th>Number of lung lesions protocolled by the radiologist as lung metastases</th>
<th>Frequency per 96 patients with preoperative CT scan</th>
<th>Percentage (%)</th>
<th>Frequency per 68 patients with postoperative CT scan</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of lung lesions protocolled by the radiologist as lung metastases</td>
<td>10</td>
<td>10.42</td>
<td>8</td>
<td>11.77</td>
</tr>
<tr>
<td>Number of lung lesions protocolled by the radiologist as indeterminate lung lesions</td>
<td>23</td>
<td>23.96</td>
<td>5</td>
<td>7.35</td>
</tr>
<tr>
<td>Number of lung lesions protocolled by the radiologist as no lung metastases</td>
<td>13</td>
<td>13.54</td>
<td>19</td>
<td>27.94</td>
</tr>
<tr>
<td>Number of lung lesions seen on imaging</td>
<td>46</td>
<td>47.92</td>
<td>32</td>
<td>47.06</td>
</tr>
</tbody>
</table>
For further information (including the results of the chest X-ray): Table 9.

**Table 9:** Presence or absence of lesions on chest CT and X-ray, displayed in frequencies and percentages

<table>
<thead>
<tr>
<th></th>
<th>Preoperative chest X-ray</th>
<th>Preoperative thoracic CT</th>
<th>Postoperative chest X-ray</th>
<th>Postoperative thoracic CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Percent (%)</td>
<td>Frequency</td>
<td>Percent (%)</td>
</tr>
<tr>
<td>Negative for lesions in the lung</td>
<td>95</td>
<td>80,51</td>
<td>50</td>
<td>42,37</td>
</tr>
<tr>
<td>Positive for lesions in the lung</td>
<td>5</td>
<td>4,24</td>
<td>46</td>
<td>39,00</td>
</tr>
<tr>
<td>Non taken</td>
<td>*</td>
<td>*</td>
<td>22</td>
<td>18,64</td>
</tr>
<tr>
<td>Missing</td>
<td>18</td>
<td>15,25</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>100,00</td>
<td>118</td>
<td>100,00</td>
</tr>
</tbody>
</table>

* In some cases, no information was available in the EPF whether a chest X-ray was taken or not. No further phone calls to doctors were made in these cases (= Missings), in contrast with chest CT.

** There were no missings for the CT imaging: in case of lacking information in the EPF, more information was obtained by making phone calls to the patients’ specialist or general practitioner (Non taken vs. Positive or Negative for lesions)
4.2.2. **Preoperative versus postoperative chest CT and X-ray imaging**

All the patients with or without preoperative lung lesions on chest imaging, were compared to their postoperative outcome of the imaging (Table 10).

**Table 10:** Comparison of preoperative and postoperative outcome of the chest imaging, displayed in frequencies and percentages

<table>
<thead>
<tr>
<th>Outcome on lung lesions</th>
<th>Type of imaging of the chest</th>
<th>CT</th>
<th>X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Frequency per 59 patients</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Preoperative + → postoperative +</td>
<td>19</td>
<td>32,20</td>
<td>3</td>
</tr>
<tr>
<td>Preoperative + → postoperative -</td>
<td>9</td>
<td>15,25</td>
<td>2</td>
</tr>
<tr>
<td>Preoperative - → postoperative -</td>
<td>22</td>
<td>37,29</td>
<td>83</td>
</tr>
<tr>
<td>Preoperative - → postoperative +</td>
<td>9</td>
<td>15,25</td>
<td>8</td>
</tr>
</tbody>
</table>
4.2.3. Diagnostic characteristics of chest CT and X-ray imaging for diagnosing lung metastases following rectal cancer

• **Results of chest CT:**

The true positive, true negative, false positive and false negative rates of chest CT were calculated (Table 11):
- Of the 46 patients that had a positive preoperative chest CT for lung lesions, 9 showed truly the presence of lung metastases, whereas 37 had no lung metastases at all.
- Of the 50 patients that had a negative preoperative chest CT for lung lesions, 2 did show the presence of lung metastases, whereas 48 truly did not have lung metastases at all.
- Of the 22 patients who did not receive a preoperative chest CT, eventually 2 did show the presence of lung metastases in the end.

<table>
<thead>
<tr>
<th></th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>19.57</td>
</tr>
<tr>
<td>False positive</td>
<td>80.43</td>
</tr>
<tr>
<td>True negative</td>
<td>96.00</td>
</tr>
<tr>
<td>False negative</td>
<td>4.00</td>
</tr>
</tbody>
</table>

Table 11: The true positive, true negative, false positive and false negative rates of chest CT
• **Results of chest X-ray:**

The true positive, true negative, false positive and false negative rates of chest X-ray were calculated (Table 12):

- Of the 5 patients that had a positive preoperative chest X-ray for lung lesions, 3 actually showed the presence of lung metastases, whereas 2 patients had no lung metastases at all.
- Of the 95 patients that had a negative preoperative chest X-ray for lung lesions, 8 did show the presence of lung metastases, whereas 87 truly did not have lung metastases at all.
- Of the 18 patients from whom the information about preoperative chest X-ray was missing, eventually 2 did show the presence of lung metastases in the end.

Table 12: The true positive, true negative, false positive and false negative rates of chest X-ray

<table>
<thead>
<tr>
<th></th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True positive</strong></td>
<td>60,00</td>
</tr>
<tr>
<td><strong>False positive</strong></td>
<td>40,00</td>
</tr>
<tr>
<td><strong>True negative</strong></td>
<td>91,58</td>
</tr>
<tr>
<td><strong>False negative</strong></td>
<td>8,42</td>
</tr>
</tbody>
</table>

The above mentioned observations were based on evolution of changes of the lesions on the chest CT or rarely by PET-CT.

From all the data collected above, the sensitivity (Se), specificity (Sp), positive predictive value (+PV), negative predictive value (-PV) and the accuracy (P) of preoperative chest CT and X-ray imaging were calculated (Table 13).
4.3. cTNM and pTNM

4.3.1. Observations

The majority of the population was clinically staged with cT2N1M0 (34.7%). Least frequent were those patients who were staged at cT4N0M1, cT3N1M1, cT2N2M0 (each 0.8%). After surgery the most common stage was pT2N1M0 (27.1%). Least frequent were pT4N1M1, pT4N0M1, pT3N2M0, pT3N1M1, pT2N2M0, pT1N0M1 (each 0.8% as well).

11 patients of the 118 didn’t have any rest tumor after resection and/or after neoadjuvant chemotherapy (T0N0/1M0). Further details and division in group staging were displayed (Table 14).

The same calculations for pTNM were applied specifically on the patients who were treated preoperatively with neoadjuvant chemoradiotherapy: ypTNM (N = 69, which is 58.48% of the total population). Usually a dose of 45 Gy (25 fractions, each of 1.8 Gy) and chemotherapy with the chemotherapeutic agent 5-FU were given to this group of patients.
Table 14: Results of cTNM and pTNM, after stage grouping, displayed in frequencies and percentages

<table>
<thead>
<tr>
<th>GROUPED STAGE</th>
<th>cTNM</th>
<th>pTNM</th>
<th>ypTNM *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency per 118 patients</td>
<td>Percent (%)</td>
<td>Frequency per 106 patients</td>
</tr>
<tr>
<td>0 (TisN0M0)</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>I (T1/2N0M0)</td>
<td>21</td>
<td>17,80</td>
<td>45</td>
</tr>
<tr>
<td>IIA (T2N0M0)</td>
<td>20</td>
<td>16,90</td>
<td>17</td>
</tr>
<tr>
<td>IIIB (T3N0M0)</td>
<td>/</td>
<td>/</td>
<td>2</td>
</tr>
<tr>
<td>IIIA (T1/2N1M0)</td>
<td>5</td>
<td>4,20</td>
<td>6</td>
</tr>
<tr>
<td>IIIB (T3/4N1M0)</td>
<td>44</td>
<td>37,30</td>
<td>9</td>
</tr>
<tr>
<td>IIIC (T4N2M0)</td>
<td>6</td>
<td>5,10</td>
<td>6</td>
</tr>
<tr>
<td>IV (T3N3M1)</td>
<td>22</td>
<td>18,60</td>
<td>21</td>
</tr>
</tbody>
</table>

* Eleven patients didn't have any rest tumor after neoadjuvant chemotherapy (TisN0M0)
The frequencies of cTNM and pTNM specifically for the 13 patients diagnosed with lung metastases were displayed (Table 15). Nine of these 13 patients received preoperative CRT.

**Table 15:** Results of cTNM, pTNM and ypTNM displayed in frequencies and percentages specifically for the patients diagnosed with lung metastases

<table>
<thead>
<tr>
<th>cTNM</th>
<th>Frequency per 13 patients</th>
<th>Percent (%)</th>
<th>pTNM</th>
<th>Frequency per 13 patients</th>
<th>Percent (%)</th>
<th>ypTNM</th>
<th>Frequency per 9 patients</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0N0M1</td>
<td>/</td>
<td>/</td>
<td>1 ( T0N0M1)</td>
<td>7.69</td>
<td>1 ( T0N0M1)</td>
<td>11.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1N0M1</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2N0M1</td>
<td>1</td>
<td>7.69</td>
<td>1</td>
<td>7.69</td>
<td>1</td>
<td>11.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3N0M1</td>
<td>1</td>
<td>7.69</td>
<td>1</td>
<td>7.69</td>
<td>1</td>
<td>11.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4N0M1</td>
<td>1</td>
<td>7.69</td>
<td>1</td>
<td>7.69</td>
<td>/</td>
<td>/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1N1M1</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2N1M1</td>
<td>1</td>
<td>7.69</td>
<td>2</td>
<td>15.35</td>
<td>1</td>
<td>11.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3N1M1</td>
<td>6</td>
<td>46.15</td>
<td>1</td>
<td>7.69</td>
<td>1</td>
<td>11.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4N1M1</td>
<td>2</td>
<td>15.35</td>
<td>2</td>
<td>15.35</td>
<td>1</td>
<td>11.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1N2M1</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2N2M1</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3N2M1</td>
<td>/</td>
<td>/</td>
<td>3</td>
<td>23.08</td>
<td>2</td>
<td>22.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4N2M1</td>
<td>1</td>
<td>7.69</td>
<td>1</td>
<td>7.69</td>
<td>1</td>
<td>11.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1N3M1</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. Discussion

Despite the increasing number of articles written on this topic, there is still no agreement about the routine use of preoperative chest CT and/or X-ray in staging patients with rectal cancer. Below, the results of the present study regarding patients with rectal cancer, were summarized and compared to other studies, which mainly consisted of patients with colorectal cancer. At the same time an attempt was made to collect the most important existing data that have already been published about this subject.

5.1. Summary of the most important results and review of relevant articles

33.90% of the total population was diagnosed with distant metastases. 16.95% showed to be synchronous metastases. This is comparable to a study carried out by Mitry et al. where 19% of the patients with colorectal cancer had detectable synchronous metastases (2). Moreover, in the present study, also 16.95% showed to be metachronous metastases. This is less than 30% mentioned by Restivo et al. (8).

11.02% of all the patients with rectal cancer were eventually diagnosed with lung metastases. In other studies approximately 5-10% of the patients with colorectal cancer also developed lung metastases at some point during or after the actual diagnosis took place (2, 7-10).

As mentioned before, the exact frequency of synchronous and metachronous lung metastases is not known (2). However, of the total population, 5.09% showed to have synchronous lung metastases and 5.93% showed to have metachronous lung metastases. Approximately half of the thirteen patients who were diagnosed with lung metastases had synchronous metastases and the remaining had metachronous metastases. Restivo et al. confirm that synchronous lung metastases, especially when isolated, are rare in colorectal cancer patients (8).

In the total population, 96 patients had a preoperative CT scan. Indeterminate lung lesions were diagnosed in 23.96% of the patients in this group. In other studies approximately 20-30% of the patients with colorectal cancer were diagnosed with indeterminate lung lesions (1).
5.2. **Diagnostic characteristics of chest CT/X-ray**

The benefit of using chest CT is its high sensitivity to detect lung metastases in comparison with chest X-ray, which has a lower sensitivity. As a result there are less false negative diagnoses of lung metastases when using chest CT. On the other hand, the specificity of chest CT is lower when compared to chest X-ray and consequently there will be more false positive results on lung metastases when using chest CT. Therefore indeterminate lung lesions on chest CT will remain a problem in staging rectal cancer.

In the present study, chest CT showed a sensitivity of 81.82%, while chest X-ray showed a sensitivity of 27.27%. This is comparable with other studies carried out by different authors where chest CT and chest X-ray showed a sensitivity of respectively 73% and 33% (12).

On the other hand, the positive predictive value of chest CT in this research was very low (19.57%) when compared to Povoski et al. who reported a positive predictive value for chest CT of 36% versus 67% reported by McIntosh et al. (8, 10).

5.3. **Differences in results of the use of chest CT and chest X-ray**

As already mentioned above, chest CT has a higher sensitivity but lower specificity than chest X-ray. The benefits of X-ray imaging that support the use of it, are the following (4):

- At the same time that chest X-ray is used to detect lung metastases, information on cardio-respiratory disease prior to surgery is provided. Griffith et al. postulated that practically only the latter might contribute to the greatest value of chest X-ray (36).
- Chest X-ray is an inexpensive technique that is easily available.
- Chest X-ray has also low associated risks.

The detection rate of lung metastases with chest X-ray was low in the present study: only 3 of the 100 patients (3.00%) were diagnosed positive for lung metastases with chest X-ray. Gielen et al. calculated that only 0.86% of the chest X-rays showed lung metastases, which is lower than the 2.9% Griffiths et al. reported in a prospective study of 208 patients. Because of the low detection rate of lung metastases by chest X-ray and the small influence on patient management, some studies do not support the routine use of chest X-ray (4).
In the study performed by Restivo et al., chest CT revealed a high number of lung lesions, of which only a small quantity were malignant (8), which is the same case in the present study. It is one of the first researches that does not support the routine use of chest CT because of the few critical influences it has on clinical practice and therapeutic decision making. They suggest that chest CT scans should be preserved for a small group of patients at high risk as judged by simpler methods of imaging (8).

Nevertheless, the potential harmful effects of preoperative imaging should not be underestimated, i.e. radiation exposure, financial costs and the consequences of possible false positive results that are multiple, e.g.: further investigations, additional financial costs, the patients' concerns about their health and delay in treatment, neoadjuvant and adjuvant therapy (1, 3).

To further investigate the difference between the use of chest CT and chest X-ray, the following question must be answered: how many patients would not have been diagnosed positive for lung metastases if only a chest X-ray and no chest CT was performed? In the present study 6 of the 13 patients with lung metastases would have been missed if a chest CT was not taken (46,15%). This seems to be a high percentage, but considering the total population of 118 this result is relatively low (5,09%).

5.4. **Difference in incidence of lung metastases between colon cancer and rectal cancer**

As already mentioned, some sources claim that patients with rectal cancer have a higher risk of developing lung metastases, unlike patients having colon cancer where a few authors suggest a lower incidence of metastases (1, 2, 11, 19, 20). This can be explained by the different routes of venous drainage (9). It has also been suggested that patients with rectal cancer therefore may benefit from a specific surveillance strategy (2).

In the present study the incidence of lung metastases in patients with *rectal cancer* was 11,02%.

Furthermore, research done by Pihl et al. showed that patients with mid and lower rectal cancers had a higher chance on developing lung metastases than colon and upper third rectal cancers because of their different routes of venous drainage (37). In this respect, Choi et al. suggest that patients with locally advanced mid and lower rectal cancer (T₃/T₄) might benefit from preoperative chest CT (9).
Kobayashi et al. reported a significantly higher risk of lung metastases in rectal cancer (7.5%) than in colon cancer (3.5%) (38). Mitry et al. calculated that rectal cancer, compared to colon cancer, had a higher risk on developing synchronous (odds ratio: 2.80) and metachronous (odds ratio: 2.63) lung metastases (2).

5.5. Shortcomings of the present study

Disadvantages associated with a retrospective study like this one are possibly the following:

- A relatively small sample size
- Some of the data were not always complete
- No control over how the data was brought together.

The interpretation of the imaging by the radiologist (e.g. defining a lung lesion as a metastasis or as an indeterminate lung lesion) and the anatomo-pathologic findings could also be biased because of the different radiologists and anatomic pathologists that have interpreted the data in the past (inter-observer variability). However, this is how it works in real life: different radiologists are involved in the reporting of imaging and different anatomic pathologists are involved in interpreting the anatomo-pathologic findings.

Furthermore, administrative tools, observers and their ideas and/or way of interpretation as well can change over time. The present study was carried out on data gathered over a period of six years and thus can also be subject to the latter.

All these obstacles could possibly be avoided in the future if more prospective studies would be carried out on this subject. In this way there would be more control over the way the information is gathered and all the variables could be set in advance to ensure the correctness of the data.

It is also difficult to compare the results of this research with those of other studies because every hospital has its own way of practice and has different kind of patients. In this respect we might speak of a selection bias: e.g. patients could be missed in the present study because of the demographic selection and difference in race, social economic status, industrial/rural regions, etc.
5.6. **Considerations**

In the present study, 6 of the 13 patients with lung metastases would have been missed if only a chest X-ray and no chest CT was performed. Considering the total population of 118 this result is relatively low (5.09%). Furthermore, the detection rate of lung metastases with chest X-ray was also low in this research (3.00%). Therefore, the routine use of preoperative chest X-ray in patients with rectal cancer is not recommended. Because of the high percentage of false positive results and the potential harmful effects associated with the use of chest CT, and because of the relatively low prevalence of lung metastases in rectal cancer, routine use of chest CT is not recommended as well. However, because the 5-year survival rate was the lowest in cTNM group stage IV (59.1%) and because of the low sensitivity associated with the use of chest X-ray, *a preoperative chest CT should be performed in patients with a high risk on developing lung metastases anyway*. In the present study high risk patients were defined as those who were diagnosed at stage cT3 and cT4. These were the two groups of patients with the highest number of lung metastases (respectively 5.09% and 1.70%). Therefore, it is important that more research is carried out in the future to further determine high risk patients.

Kirke et al. also showed that the odds of getting lung metastases increases as a function of tumor stage, and they also claim the increasing importance of a chest CT in patients with higher stage tumors (20), which was suggested by Restivo et al. as well: chest CT must be reserved for a small group of patients in whom the presence of lung metastases is more likely (8).
6. Conclusion

At this moment, the clinical value of preoperative imaging of the chest with CT and/or X-ray in patients with rectal cancer is still a point of discussion.

The present study showed a low detection rate of lung metastases in patients with rectal cancer, and therefore the routine use of preoperative chest X-ray is not recommended.

Because of the higher risk of false positive results, the potential harmful effects of CT imaging and the relatively low prevalence of lung metastases in rectal cancer, the present study does not recommend the routine use of chest CT either, except for patients with a higher risk on developing lung metastases, who in the present study were defined as patients at stage cT3 and cT4. For those patients a preoperative chest CT should always be taken to detect the presence of any lung lesions, so they can be followed more closely afterwards.

It remains of great importance that more research is done in the future to further define patients with rectal cancer who have a higher risk of developing lung metastases.

The results of the present study also confirmed a higher incidence of lung metastases in patients diagnosed with rectal cancer than in patients diagnosed with colon cancer. This could also have a great influence on the management of patients.
7. References


