

# Pulmonary Nodules and Metastases in Colorectal Cancer

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## THE FOUR ORIGINAL PAPERS ARE

1. Nordholm-Carstensen A, Wille-Jorgensen PA, Jorgensen LN, Harling H. Indeterminate pulmonary nodules at colorectal cancer staging: a systematic review of predictive parameters for malignancy. *Annals of SurgicalOncology*. 2013;20(12):4022-4030 [1].
2. Nordholm-Carstensen A, Krarup PM, Jorgensen LN, Wille-Jorgensen PA, Harling H; on behalf of the Danish Colorectal Cancer Group. Occurrence and survival of synchronous pulmonary metastases in colorectal cancer: a nationwide cohort study. *European Journal of Cancer*. 2014;50(2):447-456 [2].
3. Nordholm-Carstensen A, Jorgensen LN, Wille-Jorgensen PA, Hansen H, Harling H. Indeterminate pulmonary nodules in colorectal-cancer: do radiologists agree? *Annals of Surgical Oncology*. 2015;22(2):543-549 [3].
4. Mismatch repair and synchronous metastases in colorectal cancer: a nationwide cohort study. Nordholm-Carstensen A, Krarup PM, Morton D, and Harling H, on behalf of the Danish Colorectal Cancer Group. *International Journal of Cancer*. 2015. doi: 10.1002/ijc.29585. [4]

## BACKGROUND

### Staging

Cancer staging is the short description of a cancer at a point in its natural history that has significance in guiding treatment, in prognosis, and in comparison of end results [5].

This 40-year old definition is still valid today and staging remains fundamental in the assessment of prognosis, in the planning of treatment, in the communication between treating health

personnel and in comparison of studies on patients with cancer. Cancer staging has been called “the language of cancer” [6]. In 1928 the first known attempt to grade rectal cancer was made based on the proportion of differentiated cells in the tumour [7]. More well-known is, however, the work by C. E. Dukes, who in 1932 proposed Dukes’ classification for rectal cancer [8]. This classification was the result of observed differences in length of survival depending on the extent of the rectal cancer invading through the bowel wall and the presence of lymphatic metastases. A decade later Pierre Denoix began the development of the tumour-nodemetastasis (TNM) system that could be applied to all cancer sites [6,9] resulting in the 1st edition of the TNM classification handbook, “*Livre de Poche*”, in 1968 [10]. Today the 7th edition of the TNM (Table 1 and 2) is in use and staging is based on the further development on the initial TNM system with information on the tumour, regional nodes and metastases. The description of the anatomic extend of the disease is still central in defining cancer prognosis. This description provides the solid foundation for evaluation of the numerous new non-anatomical independent prognostic factors of recurrence and overall survival under study and is in addition to histological subtype and topographic site one of the three main axes of tumour classification [6,11]. Finally, as pointed out by Compton and Greene [12], a further advantage of the TNM system is its continuous improvement based on on-going expert reviews of existing data; it has exhaustive definitions ensuring a stringent use; and is relevant to all modern staging evaluation techniques [12,13].

**Table 1**

**Classification of colorectal cancers according to extent of the primary tumour (T stage), lymph node involvement (N stage) and distant metastases (M stage)**

T – Primary tumour	Definition
Tis	Tumour restricted to mucosa, no infiltration of lamina muscularis mucosae
T1	Infiltration through lamina muscularis mucosae into submucosa, no infiltration of lamina muscularis propria
T2	Infiltration into, but not beyond, lamina muscularis propria
T3	Infiltration into subserosa or non-peritonealised pericolic or perirectal tissue, or both. No infiltration of serosa or neighbouring organs
T4a	Infiltration of the serosa
T4b	Infiltration of neighbouring organs

N – Regional lymph nodes	
N0	No lymph node involvement
N1a	Cancer cells detectable in 1 regional lymph node
N1b	Cancer cells detectable in 2-3 regional lymph nodes
N1c	Tumour satellites in subserosa or pericolic or perirectal fat tissue, regional lymph nodes not involved
N2a	Cancer cells detectable in 4-6 regional lymph nodes
N2b	Cancer cells detectable in 7 or more regional lymph nodes
M – Distant metastasis	
M0	No distant metastases detectable
M1a	Metastasis confined to 1 distant organ or distant lymph nodes
M1b	Metastasis to more than 1 distant organ or peritoneal metastasis

Table based on 7th ed. of the Union for International Cancer Control Tumour Node Metastasis classification [18].

**Table 2**

**UICC TNM Stage Grouping of Colorectal Cancers 7th ed.**

Stage	T	N	M	5-year survival (%)
I	T1/T2	N0	M0	92.5
II	T3/T4	N0	M0	
IIA	T3	N0	M0	83.6
IIB	T4a	N0	M0	76.3
IIC	T4b	N0	M0	58.8
III	Any T	N+	M0	
IIIA	T1/T2	N1	M0	83.1
	T1	N2a	M0	
IIIB	T3/T4a	N1	M0	
	T2/T3	N2a	M0	63.8
	T1/T2	N2b	M0	
IIIC	T4a	N2a	M0	
	T3/T4a	N2b	M0	35.2
	T4b	N1/N2	M0	
IV	Any T	Any N	M+	10.4
IVA	Any T	Any N	M1a	
IVB	Any T	Any N	M1b	

UICC, Union for International Cancer Control; TNM, Tumour Node Metastasis Survival data from the Surveillance, Epidemiology and End Results (SEER) program database as published by Gao et al. 2013 [17].

### “M”

Bearing the fundamental idea of staging in mind, the introduction of the “M” to the classification of cancers is essential. A hallmark of cancer, to which the ones of colorectal origin are no exception, is the capability of invasion and metastasis [14]. About 20% of patients newly diagnosed with colorectal cancer (CRC) will have synchronous colorectal cancer metastases (SCCM), i.e. metastatic disease at the time of diagnosis [15,16].

Despite a considerable improvement of adjuvant treatment over the past five decades, the management of metastatic spread continues to be a significant challenge, and the change from localized to distant, systemic disease has great implications for the prognosis. The 5-year relative survival in patients with SCCM is 10-13%, which is considerably lower than for patients with

localized disease (Table 2) [16,17]. The treatment of patients with disseminated disease is a multidisciplinary task and most cases are not candidates for potential curative resection. However, it is of great importance to identify those patients who are suitable for metastasectomy and those in whom the metastases could become resectable after response to combination chemotherapy [19].

### Pulmonary metastases

The majority of synchronous metastases are hepatic, [15] whereas the lungs remain the most common extraabdominal metastatic location [20]. The prevalence of synchronous pulmonary CRC metastases (SPCM) ranges from 2% to 18% [20-25] and in previous studies they are most often accompanied by hepatic metastases [20,22].

Noteworthy, the risk of pulmonary involvement differs according to the location of the index tumour and has been reported to 10-18% for rectal cancers and 2-6% for colonic cancers [20-25]. The risk of pulmonary (and hepatic) metastases in colonic and rectal cancers has been attributed to the direct vascular and lymphatic communication with the intestinal tract. Furthermore, the dense capillary system in the lungs and liver acting as a filter for circulating tumour cells in combination with an especially suitable microenvironment for implantation and growth have been suggested as underlying mechanisms for the hepatic and pulmonary predilection [26,27].

Despite being the second most common metastatic site in CRC, the epidemiology and optimal treatment of pulmonary metastases have not been as intensively studied as for hepatic metastases. Pulmonary metastasectomy has been accepted as a potentially curative option in the multimodal management of pulmonary metastases despite the lack of results from prospective randomized clinical trials [28,29]. Essential for curative resection is the early detection of these metastases and selection of patients with limited number of metastases, as “complete resection based in the anatomic location and extent of disease with maintenance of adequate function is required” [28,30,31].

### Uncertainty concerning the “M” – indeterminate lesions

Given the risk of metastatic spread to the lungs and the subsequent prognostic impact, a preoperative staging of the chest with computed tomography (CT) is recommended in guidelines on the management of patients with CRC [30-33]. Though the optimal staging procedure of the lungs can be discussed, the high sensitivity for pulmonary metastases yielded by a chest CT is undisputed [34]. A concern regarding the chest CT, however, is a somewhat lower specificity and indeterminate pulmonary nodules (IPNs) are a frequent finding; in some studies detected in more than 1/3 of patients in the CRC setting [34,35]. A lung nodule is a lesion between 1 and 30 mm surrounded by normal lung parenchyma and not associated with adenopathy or atelectasis [36]. Such lesions may represent metastatic disease, [23,25,37-40] but the need for immediate treatment of the index tumour does not allow for a prospective surveillance for potential growth of these lesions on repeated CT scans. The ideal test distinguishing lesions of benign origin from the malignant ones has yet to be discovered; positron emission tomography (PET) is of limited value in the smallest of the lesions [34,41] and invasive procedures are not viable options due to the vast number of patients with IPN and technical difficulties [35,42]. Until now management has been based on guidelines on management of lesions detected in lung cancer screening [43].

The clinical significance and optimal diagnostic approach in the CRC setting remains to be resolved. Further diagnostic

workup may delay the time to resection of the index cancer, and is associated with increased radiation exposure, morbidity, costs, uncertainty among doctors and patient anxiety.

## HYPOTHESES

This thesis was set to evaluate the overall hypothesis that the initial staging chest CT in CRC patients detects pulmonary lesions in a substantial number of the patients. Lesions classified as definite pulmonary metastases have a high impact on survival prognosis, whereas “indeterminate” findings most often are benign and can be ignored in the initial decision-making on therapy for the index tumour and other metastatic sites.

- Increasing numbers of pulmonary nodules are detected with the implementation of computed tomography in staging of patients with colorectal cancer. Many of these nodules cannot readily be classified as being benign or malignant
- Pulmonary metastasectomy and/or adjuvant/palliative chemotherapy improve survival in patients with pulmonary metastases
- Clinicopathological factors and radiological characteristics are useful for evaluation of indeterminate pulmonary lesions
- The characterization of pulmonary lesions depends on the evaluating radiologist
- Analysis of biomarkers has implications in the diagnostic strategy by identification of patients in particular risk of pulmonary metastases

## AIMS

The overall objective of this thesis was to investigate the prevalence, characteristics and clinical significance of pulmonary lesions detected at the initial staging of newly diagnosed CRC patients. Lesions of interest comprised definite, synchronous pulmonary metastases and indeterminate pulmonary nodules. Specifically, the thesis addressed

- existing evidence on the prevalence of IPN and specific radiological and/or clinicopathological factors associated with malignancy of IPN
- occurrence of and risk factors for synchronous pulmonary metastases, how they are managed on a national basis and their impact on survival
- variability in radiologists’ assessment of the staging chest CT
- potential applicability of mismatch repair (MMR) status analysis of the index colorectal adenocarcinoma in an evaluation of the risk of synchronous pulmonary metastases

## PRESENTATION OF STUDIES

### STUDY I

#### **Indeterminate pulmonary nodules at colorectal cancer staging: a systematic review of predictive parameters for malignancy**

##### **Aim**

The objectives of this study were to evaluate the existing evidence regarding

1. the prevalence of indeterminate pulmonary nodules at the primary staging CT scan in patients with colorectal cancer
2. potential clinicopathological factors and radiological characteristics associated with a malignant nature of the IPN
3. clinical implications of IPN
4. the optimal follow-up regimen of IPN

##### **Methods**

This was a systematic review of original studies published in EMBASE, the Cochrane Library and Science Citation Index, PubMed databases, Google Scholar, relevant conference proceedings (United European Gastroenterology Week, American Society of Clinical Oncology, Digestive Disease Week, European Society of Coloproctology, The European Cancer Conference), trial registries (clinicaltrials.gov, EU Clinical Trials Register, the World Health Organization international clinical trials registry platform) and reference lists of relevant retrieved articles. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [44]. The literature search was performed in cooperation with the trials search coordinator from the Cochrane Colorectal Cancer Group to ensure a thorough, objective and reproducible search of the available sources. In accordance with the guidelines of the Cochrane Handbook, [45] the search strategy was set to have three sets of terms defining:

1. Participants: Patients with colonic or rectal cancer subjected to staging
2. Intervention: Primary staging computed tomography including the thoracic cavity and a follow-up intervention (not further specified) of the primary staging findings
3. Comparisons and outcomes: Definition, prevalence, characteristics and outcome of indeterminate pulmonary nodules detected at staging

In case of multiple publications on the same patient population, the most recent or complete study was selected. Records were then screened by title and hereafter by abstract. Finally, relevant articles were retrieved in full-text for further assessment of eligibility. Studies had to report the outcome of patients diagnosed with indeterminate pulmonary nodules to be included.

All studies included for analysis in the review were assessed according to the recommendations of the Oxford Centre for Evidence-based Medicine [46] and the methodology checklists developed by the Scottish Intercollegiate Guidelines Network [47]. For some of the included studies all assessment points of the methodology checklist could not be directly applied.

Weighted mean of ratios (WMR) taking the number of study participants into account were used for data analysis. The nature of the published studies did not allow for a strict diagnostic test accuracy meta-analysis.

##### **Results**

In total, 3,485 titles were screened of which 12 studies encompassing 6,222 patients were included. The study design, aim of study, level of evidence, definition of IPN and type of CT scanner varied among the studies. Assessment of pulmonary staging CT findings was reported for 5,873 (94.4%) patients of whom 732 (WMR = 9.0%) had one or more IPNs.

The risk of IPN being malignant increased with severity of UICC stage. A meta-analytical assessment of clinicopathological factors association with malignancy of IPN was deemed impossible due to the large heterogeneity of the studies.

In total, 10.8% of IPNs proved to represent CRC metastases, whereas 0.5% were primary lung cancers. The vast majority was considered to be benign lesions or remained unclarified.

Consistent findings of risk factors for IPN malignancy between the studies were few and limited to lymph node metastasis (n = 5) [38,39,42,48,49], increasing number of IPN (n = 3) [48-50] and irregular size (n = 2) [50,51], whereas calcification indicated benign IPN (n = 2) [50,51].

Finally, characteristics such as size of the IPN [51], intrapulmonary location [50], location of the index tumour [50] and presence of extra-pulmonary metastatic disease [48] were only reported to be significantly associated with malignancy of the IPN in single studies.

### Conclusion

In conclusion, 9% of patients with CRC subjected to primary staging chest CT had IPN, but only one in 100 of all chest CT staged patients have IPN ultimately proving malignant. Most pulmonary nodules were of benign origin or remained unresolved. No radiological features for IPN could be concluded pathognomonic for malignancy. Most commonly a positive nodal status was associated with IPN representing pulmonary metastases. Based on these findings, no additional work-up to IPN was recommended in addition to routine follow-up regimens.

### Limitations

Despite being a systematic and extensive review of the available literature, this study has some limitations. Despite a restrictive search strategy, the great heterogeneity of the included studies is a central challenge. This heterogeneity was due to different definitions of IPN (if any), varying diagnostic methods (type of CT scanner, expertise and number of evaluating radiologists) and no standardized follow-up regimen or time to follow-up. Furthermore, radiological and clinicopathological factors associated with malignancy of IPN were inconsistently reported. Data from the 12 included studies were unfortunately so disparate and inhomogeneous that the solidity of the conclusion is weakened.

Finally, a methodological criticism can be expressed regarding the procedure of data extraction for this study. The extraction of study results was performed solely by the first author. Two other authors verified the accuracy of the extracted data, but they were not blinded to the findings of the first author. Optimally, all authors had extracted the data independently allowing for a calculation of the level of agreement in the data extraction.

## STUDY II

### Occurrence and survival of synchronous pulmonary metastases in colorectal cancer: a nationwide cohort study

#### Aim

This study aimed to investigate

1. the occurrence of synchronous colorectal cancer metastases confined to the lungs in a nationwide cohort of Danish patients with CRC
2. to identify risk factors for these pulmonary metastases
3. to analyse their prognostic impact in terms of survival in relation to different therapeutic procedures

#### Methods

All patients with a first time diagnosis of colonic or rectal cancer registered in the Danish Colorectal Cancer Group (DCCG) data-

base between 2001 and 2011 were assessed for inclusion. Data from the DCCG database were merged with data from two other population-based registries, the National Patient Registry (NPR) and the Danish Pathology Registry (DPR). In addition to demographic and clinicopathological data on the patients, data on radiological examinations of the chest performed from 30 days before CRC diagnosis until end of follow-up were extracted from the NPR.

Risk factors for pulmonary metastases were analysed with Chi-square and Mann-Whitney-Wilcoxon tests. Multivariable logistic regression was used to adjust for potential confounding. Overall survival was assessed by Kaplan-Meier plots and stratified log-rank analysis. Furthermore, the impact of treatment measures and clinicopathological variables on survival was assessed in an extended Coxregression analysis to allow for time-varying effects of the variables [52]. A two-tailed p-value of 0.01 was used as level of significance due to the large study cohort.

### Results

In total, 40,425 patients were assessed for eligibility of whom 26,200 were included. SCCM were present in 7,742 (29.5%). Among these SPCM were registered in 1970 (25.4%). Most commonly the diagnosis of SPCM was based on radiological findings, whereas histological confirmation was obtained in 182 (9.2%). SCCM confined to the lungs (Pulmonary-only synchronous metastases, POSM) accounted for 37% (736 patients) of the UICC stage IV patients. The prevalence of POSM increased during the study period, as did the use of staging chest CT scans. The detection rate of SPCM was 7.0% (1,160 of 16,508 patients) in patients staged with a traditional chest X-ray, and 8.4% (810/9,692) in those having a chest CT staging performed.

Risk factors for POSM were advanced age, rectal cancer and a recent year of diagnosis after adjustment for potential confounders including a more widespread use of CT scans in rectal cancer patients and recent years.

Patients with POSM had an overall survival (OS) of median 376 days (IQR: 95-956), and survival was highly correlated to the therapeutic procedures performed. In patients resected for their POSM median OS reached 1470 days (95% CI: 600-1905 days), however, a pulmonary metastasectomy was only performed in 28 patients (3.8%). In total, 485 (66%) underwent resection of the index tumour, and chemotherapy (palliative and adjuvant) was administered in 367 patients (50%). Pulmonary metastasectomy, resection of the index tumour and adjuvant chemotherapy in combination had only been performed in 15 patients (2.0%). Patients having their index tumour resected (adjusted Hazard Ratio (aHR) = 0.50, 95% CI: 0.42-0.60, P < 0.001) and receiving palliative chemotherapy had a favourable survival prognosis. According to the extended Cox-regression model, the impact of chemotherapy was most notably from 30-365 days after the initial CRC diagnosis (effect day 30-365, aHR = 0.58, 95% CI: 0.48-0.70, P < 0.001), whereas the statistical significance disappeared beyond the first year after the diagnosis (effect year 1-2, aHR = 1.20, 95% CI: 0.90-1.60, P = 0.225).

### Conclusion

SPCM were detected in 7.5% of all newly diagnosed CRC patients, which is a higher prevalence than previously reported, and in 37% of the cases the metastases were solely confined to the lungs. The presence of pulmonary metastases significantly impaired survival, but both resection of the metastases and index tumour in addition to chemotherapy were associated with a prolonged overall survival.

## Limitations

The uniqueness of this study lies within the epidemiological assessment of synchronous pulmonary metastases on a national basis. However, at the same time the study design is the main limitation - allowing only associations rather than causal relationships to be explored. In particular, this impairs the strength of conclusions on the potential effect of different therapeutic measures. Additionally, these conclusions are also weakened by the limited available data on the basis for surgical intervention, adjuvant/palliative treatment and number of pulmonary metastases. Some degree of selection bias or confounding by indication must be expected regarding the observed effects of different treatment modalities.

Furthermore, few pulmonary metastases were histologically confirmed. This could be regarded as a scientific shortcoming, bearing in mind the potential difficulties in assessing pulmonary nodules; the central issue of this thesis. Some over-diagnosing may occur, as a substantial number of patients with pulmonary metastases, who were only subjected to resection of the index cancer, were still alive 5 years after diagnosis. In these cases, benign and insignificant pulmonary nodules could have been wrongly registered in the database as metastases.

## STUDY III

### Indeterminate pulmonary nodules in colorectal-cancer: Do radiologists agree?

#### Aim

The purpose of this study was to analyse

1. the variability in the radiologists' detection and characterization of indeterminate pulmonary nodules at the primary pulmonary staging CT scan in patients with newly diagnosed CRC
2. the potential associations between certain radiological characteristics as assessed by an experienced thoracic radiologist and a malignant nature of IPN

#### Methods

In the same cohort of patients as used for study II, we identified all patients referred to our centre between 2006 and 2011. By the initial cut-off date of the present study period, the use of CT scans including the chest had been fully implemented in the staging of newly diagnosed CRC patients. As for study II, data were extracted from the DCCG database, the NPR and the DPR. Patients were scanned with a 64-slice multidetector CT scanner and all scans were assessed twice. A primary assessment was performed prospectively as part of the staging procedure and planning of treatment. A vast number of radiologists performed this primary review. Secondly, an experienced thoracic radiologist, who was blinded to the primary assessment, reviewed the scans retrospectively for this study. The thoracic radiologist assessed the scans according to a preformed data extraction sheet, and classified scans into four categories: 1) normal scan; 2) benign pulmonary lesions; 3) IPN or 4) SPCM. In case of IPN or SPCM, the lesions were described in details regarding size, number, location, calcification, ground-glass opacity and consistency and the data were entered into a dedicated database. All reports from the primary assessment were retrieved in the regional Picture Archiving and Communications System and manually searched for the same information as reported by the thoracic radiologist. A research

assistant, blinded to the findings of the thoracic radiologist, extracted data from the primary scan reports to a database, which was finally merged with the data from the thoracic radiologist's review and data from the national registries using each patient's unique Danish civil registration number. Additionally, all reports on follow-up radiological examinations including the chest following the initial staging CT were reviewed in patients with IPN detected at either the primary or thoracic radiologist's report. SPCM detected at these examinations were to be located in the same location as the initial IPN to conclude that the SPCM originated from this IPN.

The level of inter-reader agreement between radiologists was tested with Kappa statistics. Radiologist performance was calculated as sensitivity and specificity. Multivariable logistic regression was used to test for association between clinicopathological variables and a malignant nature of IPN, whereas multivariable linear regression was used to assess the impact of a detected IPN on time to surgery for the CRC.

## Results

In total, 841 patients were included of whom 8.7% (n = 73) proved to have pulmonary metastases either by radiological follow-up or histological verification. IPNs were detected in 82 cases (9.8%) in the primary CT review as compared to 47 (5.6%) by the dedicated thoracic radiologist. In patients subjected to radiologic and/or invasive follow-up, IPNs were concluded to be malignant in 20/73 (27.4%, primary assessor) and 10/42 (23.8%, thoracic radiologist).

Chest CT diagnoses were consistent between the primary and thoracic radiologists in 81.8% of the cases and overall kappa was 0.49 (95 % CI 0.43–0.55), corresponding with moderate agreement [53].

Kappa for the categories "IPN" and "SPCM" were 0.31 (fair agreement) (95 % CI 0.24–0.37; P < 0.001, McNemar's test) and 0.65 (95 % CI 0.58–0.71; P < 0.001) (substantial agreement), respectively.

Time to index tumour resection was 13 days in patients with a normal scan or benign nodules only compared with 20 days for patients with IPN. Diagnosis of IPN was associated with an average surgical delay of 14 days (95 % CI 2–27 days; P = 0.029) compared with patients with normal/benign findings. None of the evaluated radiological features of the IPN as assessed by the thoracic radiologist were significantly associated with malignancy of the nodule at follow-up.

## Conclusion

A considerable number of radiologists assessed the primary CT scans and with some variability in findings when compared to a dedicated thoracic radiologist's classification. No radiological features of IPNs were found pathognomonic for malignancy of the nodule. Not surprisingly, the presence of synchronous liver metastases was associated with a higher risk of malignant nature of the IPN. Finally, time to resection of the primary tumour was prolonged in patients with IPN compared to patients with non-suspicious pulmonary CT findings.

## Limitations

There are some important limitations to this study, most of which are shared with other pulmonary nodule detection studies. First of all, the outcomes of the IPNs were determined by reviewing the results of followup radiological examinations, and only few patients were subjected to the "golden standard" histological

verification. IPNs had to increase in size and/or number to be concluded to be malignant at follow-up.

Potentially, pulmonary metastases in a patient subjected to adjuvant/palliative therapy could remain stable in size. Results are flawed if such metastases were registered as IPNs.

Some of the difference between the primary and expert review could be attributed to the implication of the radiological diagnosis made. Thus, the expert review diagnosis is “only” for study purposes, whereas the “real life” primary assessments have implications for the patient’s treatment.

Theoretically, the primary radiologist may therefore be reluctant to designate a lesion “benign” or “malignant” definitively.

Further limitations can be attributed to the retrospective design of the study. Not all patients were subjected to a standardized follow-up regimen or time to follow-up radiological examination. A prospective design could have allowed for an assessment of the impact of an indeterminate finding and subsequent examinations on quality of life and potentially a cost benefit analysis of such additional examinations.

Due to limitations regarding both radiological resources and number of CT scans we were not able to have another dedicated thoracic radiologist to do a re-review of the CT scans. It would have been interesting and indeed scientifically relevant to control for the “expert”. With an estimated proportion of disagreement between two “experts” of 0.1 the sample size of scans to be reviewed by a second “expert” would be 1,603 with a set kappa of 0.8 and a 95% CI from 0.75-0.85.

## STUDY IV

### Mismatch repair and synchronous metastases in colorectal cancer: a nationwide cohort study

#### Aim

This study aimed to investigate,

1. whether the routinely assessed MMR status of the colorectal tumour was associated with the localization of synchronous metastatic disease as this could be valuable in the assessment of IPN on the staging CT
2. and the impact of MMR on survival in patients with stage IV disease

#### Methods

As for study II and III, the patient cohort was identified in the DCCG database, and data from the DCCG were merged with data from the NPR and the DPR. This study evaluated all patients with a first time diagnosis of CRC between 2010 and 2012 for inclusion. Patients with histologically verified colonic or rectal adenocarcinomas in whom MMR protein expression (MLH1 and MSH2) analysis was performed by immunohistochemistry (IHC) were eligible.

Data on histopathology were extracted from the DPR. Trained pathologists assessed all specimens according to the TNM 5th Edition. The mismatch repair analyses using IHC followed the guidelines from the Nordic Immunohistochemical Quality Control [54].

Associations between variables and synchronous metastatic disease were analysed with the Chi-square and Mann-Whitney-Wilcoxon tests for categorical and continuous variables, respectively.

Multivariable and multinomial logistic- and Cox-regression and proportional excess hazards analyses were used for con-

founder adjustment and to adjust for the general population mortality.

#### Results

In total, 6,692 patients with complete registration of MMR status were included. A deficient MMR occurred in 983 of the patients and was more common in females, in elderly patients, in proximal tumours and in distinct histological subtypes. The risk of venous invasion or lymph node metastasis was lower in patients with deficient MMR compared with a proficient status.

SCCM were present in 935 patients in the final study cohort (14.0%). Liver (566/935, 60.5%) and pulmonary metastases (204/935, 21.8%) were the most common metastatic locations. One hundred twenty-four patients had multiple metastases, the majority having hepatic metastases as well (117/124, 94.4%). Metastasectomy was performed in 30 (14.7%) with pulmonary metastases.

Patients with dMMR had a decreased risk of having SCCM, OR = 0.54, 95% CI: 0.41-0.71,  $P < 0.001$ . dMMR was associated with a decreased risk of liver metastases in multinomial logistic regression (OR = 0.30, 95% CI: 0.18-0.49,  $P < 0.001$ ), but no statistical significant association was found for either pulmonary metastases (OR = 0.71, 95% CI: 0.39-1.29,  $P = 0.258$ ) or metastases in both liver and lung (OR = 0.26, 95% CI: 0.26-1.77,  $P = 0.436$ ).

Finally, we found that dMMR had no significant impact on survival in the univariable Coxregression analysis, HR = 1.24 (95% CI: 0.91-1.70,  $P = 0.166$ ), or in the univariable proportional excess hazards analysis, HR = 1.26 (95% CI: 0.90-1.76,  $P = 0.183$ ). Nor did MMR status influence survival in the multivariable analyses.

#### Conclusion

Patients with dMMR had decreased risk of synchronous metastatic disease, but the association was limited to hepatic metastases. Survival in stage IV patients was not influenced by MMR status.

#### Limitations

Due to the methodological similarities with study II the present study has some of the same limitations.

Additionally, the recommendations for MMR immunohistochemistry (IHC) were revised during the study period resulting in a relatively younger patient population in the beginning of the study period. Secondly, only 75% of the patients eligible for the study were MMR IHC tested. These two points may result in some degree of selection bias.

Deficient MMR tumours were presented as a single entity. This may be an oversimplification.

It is well-known that tumour morphology and behaviour depend on the etiology of the MMR deficiency and the secondary mutations resulting from microsatellite instability [55].

The number of deficient MMR tumours may be slightly underestimated due to the IHC testing applied. IHC detects about 95% of MMR deficient tumours. A missense mutation in the MLH1 gene can result in a non-functional, but IHC detectable protein [56].

Finally, the risk of a type II error regarding the significance of MMR status on pulmonary metastasis should be kept in mind. Few patients had confined pulmonary metastases relatively to patients with hepatic metastases and only few of the pulmonary metastases were histologically confirmed. One should take caution to give definitive conclusions on the impact of MMR status on extra-hepatic metastasis.

## METHODOLOGICAL CONSIDERATIONS

This thesis is largely based on prospectively collected data from the DCCG database. In this section some aspects of the methodological approach to handling these data for this thesis will be discussed. The approaches were similar in studies II, III and IV, and will be described collectively, though small differences existed regarding the relevant study period and demography to satisfy the individual study objectives, availability of CT scans and data from other databases.

Data have been prospectively collected in the DCCG database since the 1st of May 2001 on all newly diagnosed colorectal cancer cases in Denmark to survey that the quality of CRC treatment adheres to the desired clinical standard [57]. Furthermore, as the patient completeness is currently >98%, [58] the collection of uniform and standardized data enables the conduction of nationwide, epidemiological studies representative for the Danish population with low risk of selection and referral bias [59]. Previous random checks have found a high validity of the DCCG data [60]. A monthly linkage to the NPR serves to validate the completeness of data.

All surgical departments register data on patients with newly diagnosed CRC prospectively into the database and departments are notified of missing data and logical errors in the data reporting [61].

Data on all patients in the DCCG database were additionally retrieved from two other nationwide patient registries: the NPR (registry of all patients admitted to Danish somatic hospitals, emergency rooms, and outpatient clinics) and the DPR (registry of all individuals in Denmark who have had a histological examination of tissue, cell, or autopsy material) [61]. The link between three nationwide databases served as a source for identification of confounders not registered in the DCCG database. Importantly, this merge also served as a validation of variables registered in the DCCG database. In case of a mismatch between the databases on specific key variables, a manual search in the pathology and patient registries, patient records and radiology reports (if available) was conducted. The key variables included the diagnosis of CRC, date for the (first time) diagnosis of CRC, UICC stage at the time of diagnosis and course of treatment. The merge of data across different registries is uncomplicated due to the unique and personal civil registration number, given to all Danish citizens at birth. The merge and management of data was conducted centrally by the DCCG's database manager to ensure clean datasets for statistical analyses.

Though the DCCG database has been reported sufficient quantitatively as well as qualitatively, the accuracy of the metastatic coding is not known. Potential under- and over-recording of metastatic spread could lead to biased estimates of association. Therefore a further validation on the registration of synchronous metastatic disease was deemed essential to fulfil the objective of the thesis.

Additionally, this validation sought to ensure that registered metastatic disease was actually synchronous and most likely did originate from a colorectal cancer.

### The primary tumour

It was of paramount importance for inclusion, that patients had a histological verification of their colorectal cancer. Histological verification on the diagnosis was obtained from the DPR. If a patient had not been subjected to surgery or any other histological examination, the diagnosis of a malignant colorectal tumour had to be verified by a trained colorectal surgeon for the patient

to be included. In these cases the CRC diagnosis in the DCCG database had to correspond to a CRC diagnosis in the NPR.

Only patients with a first-time diagnosis of CRC from the commencement of CRC registration in the DCCG database from 2001 and onward were included. The patient was excluded in the case of a previous registered specimen in the DPR suggesting CRC to minimize the risk of analysing data on recurrent CRC cases or metachronous metastatic disease. Furthermore, this was done to ensure that data from the registries concerned the primary staging.

### Metastases

Synchronous metastatic disease was defined as any detected metastases within a timeframe of 30 days prior till 120 days after the diagnosis of the index cancer. There exists no definite consensus regarding the definition of synchronous and metachronous metastases. The four months' time range is in line with the "time of staging data" according to the American Joint Committee on Cancer [18]. In the literature "synchronous" represents lesions detected both at the time of resection of the index cancer, and within 3, 6, or 12 months from the diagnosis of the index cancer, but the term is often not precisely defined [62-66]. According to medical dictionaries "synchronous" refers to lesions or conditions at times of an event of interest [67]. In the given case, the event of interest is the primary staging. We defined the primary staging as any diagnostic work-up performed 30 days prior- till 120 days after the diagnosis of the index cancer. It is the assumption that any detected metastatic spread within 120 days from the diagnosis was present at the time of the CRC diagnosis even though it was not detected at this point.

Indeterminate hepatic and/or pulmonary lesions detected at the staging procedures should not be registered as metastases in the database according to the DCCG registration guidelines. Applying a timeframe for detection of "synchronous" metastases therefore allows for a follow-up CT scan for clarification of such potential indeterminate lesions at three months, which is clinical practice in some Danish colorectal cancer centres. Subsequent examinations were assumed to control for recurrent disease in patients not previously registered with disseminated disease. The DCCG database holds no information on recurrent/metachronous disease. The 30-days limit prior to the diagnosis of the CRC is somewhat arbitrarily, but ensured that all relevant diagnostic procedures in the staging process could be identified in the NPR.

None of the patients in the database had metastases registered prior to these 30 days. An epidemiological criticism to this timeframe is the diagnosis of synchronous metastases in patients with a follow-up shorter than 120 days. Potentially, some patients may die within these 120 days and thereby before the final diagnosis of synchronous metastatic disease.

A validation of registered pulmonary metastases was performed on data obtained from the DCCG database as the accuracy of the "pulmonary metastases" diagnosis is of paramount importance for this thesis. As stated above, only definite pulmonary metastases on radiological and/or histological evaluation are to be registered in the DCCG database – not indeterminate findings.

The DPR was scrutinized for any histological confirmation of metastatic disease. In most of the cases this "golden standard" verification could not be obtained. Therefore data on all radiological procedures performed during the primary staging period were extracted from the NPR. Patients were excluded if they had no histological verification of a pulmonary lesion or no relevant radiological procedure.

The DPR was also reviewed for data on other metastases than pulmonary registered in the DCCG database, but no equivalent restrictions on diagnosis of these extra-pulmonary metastases in relation to radiological or surgical procedures were applied.

We used the DPR to detect synchronous metastatic disease in the cases where no information was available in the other registries regarding the cancer stage at diagnosis. Patients whose cancer stage remained undetermined were excluded as the stage of the disease is essential to all aspects of the included studies.

### Other cancers than CRC

Patients with other cancers than CRC (except for non-melanoma skin cancers) five years prior till five years after the CRC diagnosis were excluded. It has been argued that patients with multiple malignancies will become an increasingly important topic in cancer epidemiology due to an increasing number of cancer survivors [68]. Liu et al. found that 9% of patients with an initial CRC develop a subsequent malignant disease.

In an epidemiological perspective it would have been interesting to have the covariate "Other cancer" available for the multi-variable analysis. Patients with concomitant cancers were, however, excluded for several reasons. In some cases other cancer forms had initially been interpreted as CRC and faulty entered in the DCCG database, typically non-CRC with invasion to the rectum or colon and anal cancers registered as rectal cancers. In other cases histological sampling of what was thought to be dissemination of the CRC revealed other cancers – e.g. histological sampling of pulmonary metastases revealing primary lung cancers.

A review of all cases with specimens registered in the DPR was undertaken in cooperation with an experienced gastrointestinal pathologist to determine whether the histological subtype was consistent with CRC in each case. Additionally, a review was done in all cases registered with another cancer than CRC in the abdomen or thoracic cavity to identify cases where potential direct invasion or metastases from the CRC erroneously had been registered as another cancer. Despite the initial intention to include all patients in the DCCG database and potential epidemiological concerns, it was deemed necessary to exclude patients with evident other cancer than CRC after these reviews to ensure that 1) patients actually had CRC, 2) metastases did originate from the CRC and 3) that data on oncological treatment extracted from relevant databases concerned the CRC.

## DISCUSSION

### Principal findings

Pulmonary lesions are common at the initial staging of colorectal cancers, and the frequency has increased with the introduction of computed tomography scans. Few of the lesions were histologically confirmed. The accuracy of the radiological characterization is therefore of paramount importance. Survival prognosis for the increasing number of patients registered as having a definite pulmonary metastasis was severely impaired. However, the detection of these metastases is important as some patients can be cured with metastasectomy and others may benefit from palliative chemotherapy and resection of the index cancer. The metastatic disease was confined to the lungs in more than 1/3 of the patients with pulmonary metastases.

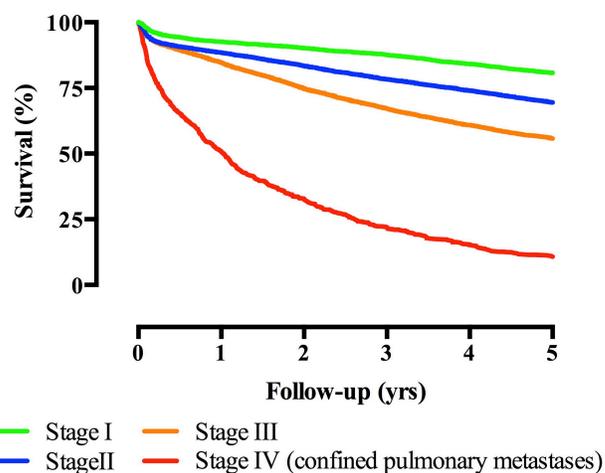
Unfortunately, a substantial number of the pulmonary nodules cannot be classified as metastases or insignificant benign lesions at the time of the staging. The number and clinical signifi-

cance of these indeterminate nodules depend on the evaluating radiologist. The risk of malignancy was about 10% in a systematic review of previous study results compared with 20% of IPNs detected at a CT review by an experienced, thoracic radiologist of a local cohort of more than 800 consecutive patients with newly diagnosed CRC. The CT staging scan has a high specificity for pulmonary metastases, but the sensitivity is impaired due to the indeterminate lesions. Despite multiple studies no pathognomonic radiological feature for malignancy of an indeterminate pulmonary nodule exists. A rectal index cancer, liver and lymph node metastases, tumour deposits and venous invasion are factors associated with pulmonary spread, however, their use in the management of IPNs remains uncertain. Potentially, biomarkers could be of some value in determining the true nature of these indeterminate lesions. Mismatch repair status had no significant impact on the occurrence of synchronous pulmonary metastases and is therefore unlikely to have value in the clinical management of IPNs.

### CRC and the metastatic process

Colorectal cancer (CRC) is a significant cause of morbidity and mortality worldwide. In 2012, Global Cancer Statistics estimated more than 1.3 million incident cases and almost 700,000 deaths from CRC [69]. According to the Danish Cancer Registry more than 4,400 patients were diagnosed with colorectal cancer in Denmark in 2011 [70]. Hence CRC was the third most commonly diagnosed cancer in Danish men and second in Danish women, and the third most common cause of cancer death in both genders [70]. Approximately 90% of all deaths in patients with CRC are due to metastatic dissemination [71]. Early detection is of paramount importance with regards to the chance of cure, however, at presentation 15-25% of the patients will have metastatic disease [72]. Figure 1 depicts 5-year survival for patients with confined synchronous pulmonary metastases in comparison to survival for patients with UICC stage I-III disease at the time of diagnosis.

Figure 1



Survival according to UICC stage (based on study II data) [2]

Colorectal cancers are heterogeneous. Despite being the best-examined tumour entity little is known about the molecular determinants for metastasis [71]. Stable frequencies for dissemination to specific target organs has been argued to suggest for a molecular background of the metastatic tropism [72]. The majority of colorectal cancers are adenocarcinomas developing from benign precursors, adenomas, in a multi-step process of muta-

tions and epigenetic changes in tumour suppressor genes and oncogenes [73]. Since the first model of colorectal carcinogenesis more than 20 years ago, [73,74] it has become clear that CRC develops through several heterogeneous molecular pathways [75-77]. Awareness of this heterogeneity is important, as it may have consequences for the metastatic potential of the CRC [78,79].

The understanding of metastasis, the shift from localized to systemic disease, is essential in CRC therapy and is necessary to address for future intervention and prevention strategies [6]. More than a century ago Paget described the metastatic process in botanical terms, the so-called seed-and-soil theory, in which the distribution of the metastases is not simply a matter of chance [80]. The primary tumour as well as the predilection site for metastases could possess specific properties that predispose secondary growth at specific locations [72]. Though the underlying molecular abnormalities for CRC carcinogenesis have been extensively investigated, little is known about the determinants for the metastatic formation [71]. The traditional perception of metastasis in CRC has therefore adhered to the cascade hypothesis, in which the liver is affected firstly as most of the venous blood from the colon enters the portal vein and thereby transfers cancer cells to the liver capillaries [81-83]. Subsequently, pulmonary metastases arise from liver metastases and finally, arterial metastases develop from the pulmonary metastases [83,84].

### Pulmonary metastases

Blalock is often credited for performing the first pulmonary metastasectomy in colorectal cancer in 1944 [85].

Actually, this paper refers to a pneumonectomy of a lung co-incidentally affected by CRC metastasis. At this time surgery in the treatment of pulmonary metastases were regarded as obsolete as the disease had escaped the "first" hepatic filter and thereby was systemic [86].

Today national and international guidelines recommend pulmonary metastasectomy when possible [30,31,87]. A survey of the current practice among members of the European Society of Thoracic Surgeons found that pulmonary metastasectomy represents up to 10% of the surgical activity and was performed by 99.3% of the responders in the CRC setting [88]. Criteria for surgical intervention adhere to the principles introduced in 1965 by Thomford et al. and require that primary tumour is under control, no extrathoracic lesions are present (except for resectable liver metastases), the metastases appear technically resectable, and the general and functional risks are tolerable [89]. The practice of pulmonary metastasectomy is based on mainly retrospective data of highly selected patient series despite a widespread conduction and guideline recommendation of surgical intervention [90]. These studies report 5-year survival rates of up to 40-60% [90]. This prognosis is in line with the results of study II, however, only a small fraction of the patients were subjected to pulmonary resection and the results are most likely affected by selection bias or confounding by indication. The first randomized trial, Pulmonary Metastasectomy in Colorectal Cancer [PulMiCC] is currently being undertaken [91]. An optimal assessment of the therapeutic strategy in these patients necessitates further clarification of the underlying epidemiology and controversies in the optimal diagnostic approach.

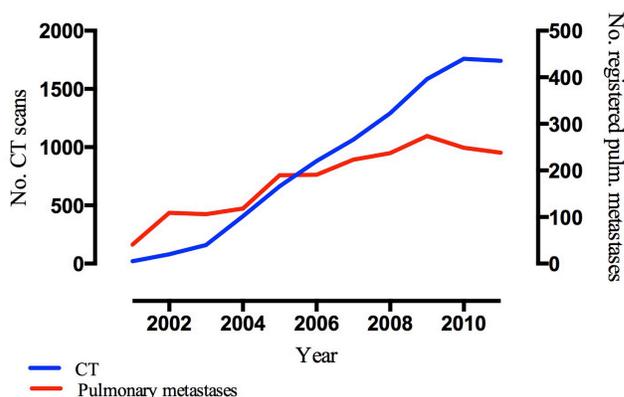
### Trends in detection

In concordance with the cascade hypothesis and previous findings, the lungs were the second most common location for synchronous metastatic spread in CRC, only surpassed in number by

liver metastases [2,15,20]. It is well established that the lungs are the most common extra-hepatic location for disease recurrence,[92] but data on synchronous presentation on pulmonary metastases are more scarce [20,22,65]. In this thesis, the prevalence of synchronous pulmonary metastases was investigated for the first time on a nationwide basis. Mitry et al. [20] investigated the epidemiology and prognosis of colorectal cancer in a French regional cohort from 1976 to 2005 and discovered a nearly three-fold increment in the estimated prevalence of SPCM. Despite an earlier diagnosis over time, the occurrence of metachronous pulmonary metastases (in patients resected for cure and followed with a yearly chest X-ray for 5 years) did not change during the study period [20]. These trends were attributed to an increasing use of CT-scans over time though data on the staging procedure were not available. In 2005 pulmonary staging with CT scans were not fully integrated at all centres treating CRC in Denmark. As found in the French study the continuous implementation of chest CT following national guidelines was associated with an increased number of registered SPCM.

The use of preoperative staging with CT of the chest increased significantly from 9% in 2001–2004 to 63% in 2009–2011 with a concomitant increase in the number of registered pulmonary SCCM from 5.0% to 9.3% (Figure 2). The increasing application of CT can only explain the increased registration of pulmonary metastases in part. Other potential determinants cannot be extracted from our available data, but an increased awareness and concomitant registration of pulmonary metastases, increasing experience of evaluating radiologist and improving scanning technology (e.g. the introduction of multi-slice scanners) may be of importance.

Figure 2



Number of staging chest CT scans and synchronous pulmonary metastases in the Danish CRC cohort from 2001-2011

### Staging chest CT - pro et con

The necessity of a sensitive pulmonary staging modality is underlined by the prognostic effect of the detected pulmonary metastases and the fact that >90% of these metastases are solely based on a radiological diagnosis. Furthermore, a high accuracy of the staging is important to avoid firstly unnecessary surgery in patients with no lung metastases, and secondly the potential exclusion of patients with a surgically curable disease from a potential beneficial procedure.

Today a preoperative staging chest CT is recommended in the DCCG's guidelines, [32] the National Comprehensive Cancer Network guidelines for both colonic and rectal cancer [30,31] and the Association of Coloproctology of Great Britain and Ireland [33]. In the position paper from the European Registration of Cancer Care multidisciplinary consensus conference in 2012 it is stated for colonic cancer staging: "Chest-CT as routine work-up is recommended; although there is evidence that a chest X-ray may be used for routine work-up" and in the section for rectal cancer staging "Abdominal CT, chest X-ray or CT are the minimal requirements for staging of distant metastases. Thoracic and abdominal CT are recommended as part of the staging protocol to detect distant metastases, especially for high risk rectal cancer" [93]. Despite being fully integrated in the diagnostic work-up, the value of a routinely performed staging chest CT has been subject to much debate. This is also the reason why chest X-ray is still accepted in the diagnostic work-up as listed above. It is well established that the pick-up rate of pulmonary metastases is higher in CT than conventional chest X-ray [34]. This is due to a higher spatial resolution and the lack of superimposition, and CT detects smaller nodules at an earlier time [94].

However, sceptics doubt any beneficial clinical implications of the higher detection rate. Furthermore, concern is raised regarding the possible delayed treatment, prolonged anxiety and additional diagnostic procedures with accompanying cost and radiation exposure due to a vast number of indeterminate pulmonary lesions on CT [24]. A review of studies comparing chest CT and chest X-ray found limited evidence for using chest X-ray [34]. The implications of the higher detection rate by CT were, however, unclear [34]. In the setting of metachronous pulmonary metastases early detection by CT accompanied by aggressive resection has been associated with favourable survival prognosis, [95] whereas yearly chest X-ray is of questionable value [96]. These surrogate markers for the effects of chest CT and X-ray may not be directly translated to a statement regarding their relevance in the detection and treatment of SPCM. SPCM may imply a more aggressive disease with poorer survival rates than in patients with metachronous lesions, [97] but as for metachronous lesions early detection before further dissemination may improve the chance of curative surgery [90,98]. Some authors propose that chest CT

should be reserved for high-risk patients; i.e. patients with rectal cancer, liver metastases or node positive disease [21-24,99,100]. Unfortunately, even patients with early stage CRC develop pulmonary metastases and 37% of patients (as found in study II) with pulmonary involvement will have no detectable extra-thoracic dissemination. Tan et al. found an incidence of 5.9% of isolated pulmonary metastases in patients with colonic cancer [22].

The true value of a chest CT can only be assessed in a prospective study where the initial surgical intent is known before further investigations are performed. A value of the initial staging CT (often not discussed) is its use as a baseline study in the routine follow-up after 12 and 36 months (according to Danish guidelines [101]) from the radical resection of the index tumour.

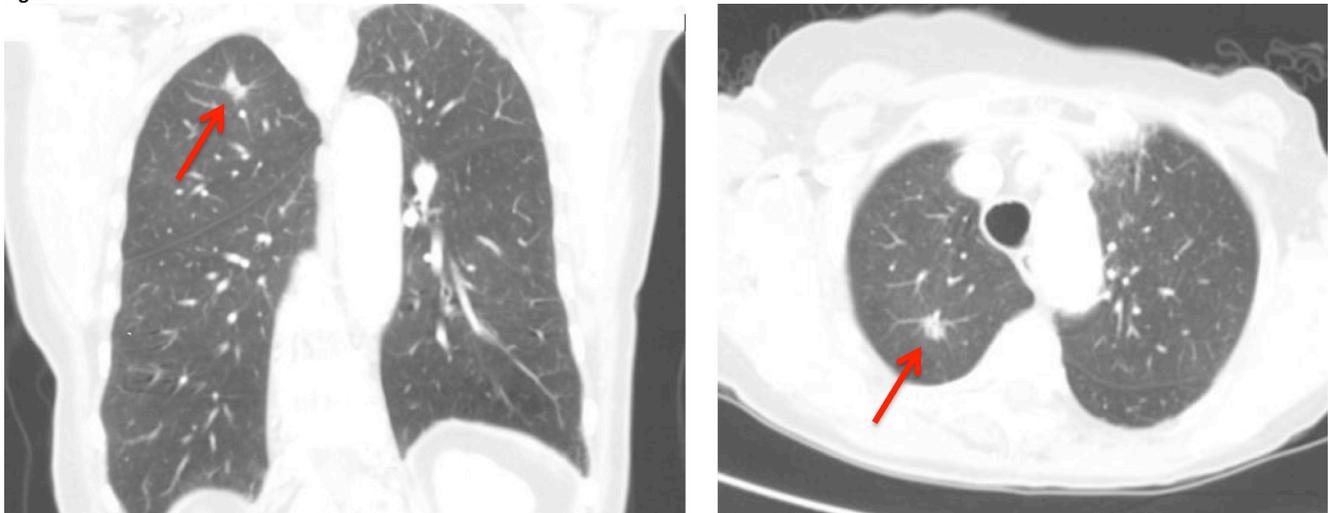
As chest CT is currently fully integrated in our national guidelines and everyday clinical practice a discussion on its relevance in staging in relation to CXR has become obsolete. Rather, future focus may be on the potential introduction of PET/CT into pulmonary staging. The identification of patients in high risk for pulmonary metastases may, however, still be of great importance in relation to the staging CT; not for the preclusion of scans in some patients, but for additional guidance, when indeterminate lesions are encountered.

#### Indeterminate Pulmonary Nodule

Pulmonary metastases may present in numerous ways on chest CT. A simple exhaustive and complete definition of a pulmonary metastases in colorectal cancer based on radiological features cannot be given. As most of the radiological features are unspecific for metastases and no pathognomonic characteristics exist, a substantial number of the pulmonary nodules cannot readily be classified as either benign or malignant impairing the specificity of the CT. Often the nodules of metastatic origin are rounded lesions of soft tissue attenuation varying in size, well-circumscribed and located in the periphery and lower parts of the lungs [102].

As for other adenocarcinomas, pulmonary metastases of colorectal origin may present as single lesions. The presence of multiple pulmonary nodules in patients with a known extra-thoracic malignancy typically indicates pulmonary metastasis, but radiological characteristics remain unspecific; especially when only single lesions are encountered [102]. The radiological appearance

Figure 3



Solitary Indeterminate Pulmonary Nodule (red arrow) detected at staging CT scan

of pulmonary metastases may furthermore depend on the route of dissemination [103].

Most metastatic nodules are less than 1 cm in diameter, but increasing size of pulmonary nodules has been associated with elevated risk of malignancy [51,104]. Growth characteristics of metastatic nodules vary (even in the same patient) and volume doubling time has been reported from 11 to 150 days for colorectal cancer [105]. Growth is a feature that can be altered when chemotherapy is administered. This also applies to calcification and cavitation of the nodules, which may be too unspecific findings to differentiate malignant nodules from benign ones [102]. Furthermore, the metastases may have atypical radiological manifestations making the diagnosis even more difficult [106]. The diagnostic criteria for evaluating and managing pulmonary nodules adhere to the recommendations developed in lung-cancer screening trials [43,107,108]. The a priori risk of pulmonary malignancy in a patient with a colorectal cancer is not comparable to a participant in a lung-cancer screening study and these guidelines may not be directly applied to the CRC setting. Interestingly, in a lung-cancer screening trial the prevalence of small, non-calcified pulmonary nodules detected on CT was 51% [108].

Recently additional studies in the colorectal cancer setting have been published [3,100,109-114]. Results still vary and external validity of these mainly retrospective, single-centre studies are impaired by different definitions of IPNs, type of imaging performed, patient characteristics, presence of extra-thoracic metastases, varying inclusion of metachronous nodules were included and exclusion of some nodules with specific morphological features. Furthermore, results are impaired by varying follow-up regimens and definitions of a malignant outcome of the nodules and rarely include a histological verification.

#### **Management of IPN – evaluation of existing guidelines**

Some studies on IPN in the CRC setting have strived to develop guidelines on the management of IPN. Gomez et al. [111] presented a strategy for management of pre-operatively detected IPNs in patients evaluated for resection of liver metastases. Briefly, patients with resectable liver disease were resected and reassessed with a PET/CT after three months. If patients had borderline resectable liver metastases they were recommended to have a PET/CT prior to potential liver metastasectomy. Baek et al. [115] failed to establish follow-up guidelines in patients with rectal cancer and IPN due to few patients having pulmonary metastases at follow-up. They suggested a longer follow-up period for patients subjected to FOLFOX therapy than those treated with 5-FU alone or no chemotherapy, as the time to development of pulmonary metastases was longer in patients in FOLFOX treatment. However, this time difference was not statistically significant and the recommendation is based on a very limited patient cohort. Nor could Kim et al. [110] definitively conclude that adjuvant therapy had impact on the time to progression of IPN into definite malignant lesions. In this study five risk factors for malignant progression were identified being: metachronous IPNs, a rectal index cancer, a higher nodal stage, bilateral lung involvement, and perineural invasion. These factors were used to construct a risk prediction model according to which the follow-up of IPN could be individualised from no further follow-up to repeat CT scans with 3 months interval. Unfortunately, perineural invasion and nodal status may not necessarily be known in the pre-operative planning.

Little attention in previous studies and guideline proposals has been given to the experience of the evaluating radiologist, though exactly this experience is commonly listed as one of sev-

eral reasons for varying results between studies on IPN. In study III the inter-reader variability in the detection and characterization of pulmonary nodules on CT scans was found to be substantial. This is in line with results from other setting than CRC [116-118]. A pulmonary nodule initially characterized as indeterminate may be reclassified as either benign or malignant in a second radiological review [35,119]. Even between expert radiologists the definition of “truth” may vary [116]. A challenge in everyday clinic is the inadequate accessibility of dedicated thoracic radiologists for assessments of all staging chest CTs. This issue could be reduced if a second review, by a group of experienced thoracic radiologists, of the scans with IPN was performed. In total, only 10% of the staging scans in the study III would have had to undergo a review by dedicated thoracic radiologists. Of course, the feasibility and value of this approach needs to be validated in a prospective trial.

#### **Management of IPN – proposal of new guideline**

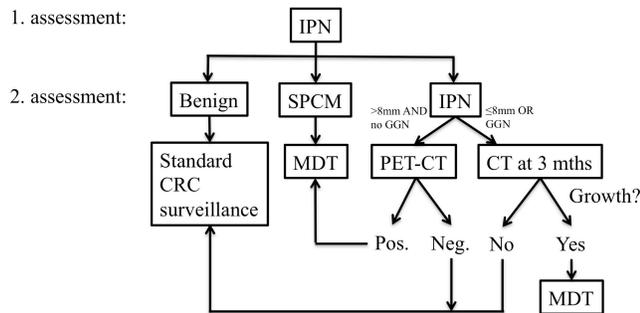
Because IPNs are most likely of benign origin, further diagnostic work up of the nodules should not postpone the treatment of the index tumour; patients should be treated “in the benefit of doubt”. Preferably treatment planning is based on the assumption that IPNs are not malignant and are followed with serial imaging. Additional pre-operative work-up has been proposed in patients with borderline resectable liver metastases as stated above [111]. The lack of a consensus in the definition of IPN and varying CT techniques utilized make it difficult to make a single omnipotent management guideline with great external validity in the CRC setting. Pre-operatively known clinicopathological factors (besides synchronous liver metastases) and radiological characteristics to be used in the risk assessment of IPN are unconvincing. It has been stated, that nodule size is the only measurable factor on chest CT [110].

Bearing these results in mind and the fact that the level of experience of the evaluating radiologist is a decisive parameter in the assessment of IPN (as found in study III), it may be relevant to take the inter-observer variance into account when management guidelines of IPNs are submitted. In Figure 4 a management strategy of IPN is put forward.

It seems clear that some nodules possess obvious signs of malignancy or benignity. The patient should be subjected to the multidisciplinary team (MDT) conference with representatives from abdominal and thoracic surgery, oncology, pathology and radiology if there is evidence of pulmonary metastases. No further follow-up is necessary besides routine CRC surveillance if the nodule is clearly benign. In the case where an IPN is encountered in the primary CT review, the scan is to be assessed by a group of dedicated thoracic radiologists. This will reserve the limited availability of thoracic radiological expertise for a subset of the staged patients. The secondary review will determine the following work-up. If pulmonary nodules are still deemed “indeterminate” at the second review, the patient is subjected to a low-dose follow-up CT at 3 months interval or a PET-CT, depending on the size and presence of ground-glass morphology. A ground-glass nodule is, according to the Fleischner Society, a focal nodular area of increased lung attenuation through which normal parenchymal structures can be visualized, sometimes referred to as a “sub-solid” nodule [120]. A suspicion of malignancy may persist despite a negative result in some of the smallest nodules being PET-CT scanned. These patients may be subjected to a low-dose CT at 3 months interval as well to determine the potential growth rate of the nodule. A nodule that appears stable in size in similar projections in a CT scan is considered more likely benign [121]. In the

absence of growth or new nodules, we suggest that the patient can be allocated to the standard follow-up regimen for the treatment of the index cancer.

**Figure 4**



**Management of Indeterminate Pulmonary Nodules.**

IPN, indeterminate pulmonary nodule; SPCM, synchronous pulmonary metastases; GGN, ground-glass nodule; MDT, multidisciplinary team conference; CT, computed tomography

According to the DCCG this includes a CT of the chest and abdomen at 12 and 36 months after a curative resection, [122] which allows further assessment of the nodule for more than the recommended 2 years with respect to the tumour growth kinetics of adenocarcinoma [43,121,123]. This would also be sufficient for a potential delay in time to progression of IPN in the case of adjuvant chemotherapy [110,115]. In few cases the MDT can decide to subject the patient to a CT guided core biopsy. This is particularly useful for peripheral lesions and has been reported to have a moderate specificity, but high (>95%) sensitivity for malignant lesions [124]. The need of a tissue diagnosis should, however, be weighed against the risk of pneumothorax and hemorrhage [121,124]. Once again, it is of outermost importance in any proposed guideline for the management of IPN detected at the primary CRC staging that IPN and the relevant diagnostic work-up should not per se delay the treatment and can initially be disregarded in the treatment of choice.

**Management of IPN – in search for the future guideline**

The management strategy as proposed above is rather simple and pragmatic. Optimally, reproducible and objective patient and nodule characteristics could aid to determine the further work-up and treatment of patients with IPNs [125]. “Pulmonary Nodule Malignancy Risk calculators” based on Bayesian analysis, as developed for educational use, [126,127] are desirable. The diversity of radiological presentation forms of pulmonary metastases and the absence of radiological features in IPN of malignant nature limit the use of radiological characteristics in the risk prediction for a malignant nature of IPN.

Not surprisingly, characteristics of the CRC already known to be associated with metastatic spread to the lungs are also found to be associated with an elevated risk of an IPN being malignant at follow-up [38,39,42,48-50,100,109,110]. Known risk factors such as rectal index cancer, lymph node spread and hepatic involvement should warrant a high degree of suspicion of pulmo-

nary metastases. However, these factors remain unspecific and their potential role in the management of IPN is yet to be defined.

Despite the association between a rectal cancer and pulmonary metastases in study II more than 50% of the patients with synchronous metastases confined to the lungs had an index cancer in the colon.

The determinants for metastatic spread relate to anatomical features but are modulated by tumour-host interactions that are currently not fully understood, in line with the seed-and-soil theory.

Whether such tumour-host interactions underlie some of the discovered association in study II such as between increasing age and pulmonary metastasis remains speculative. Interestingly, lower age was associated with hepatic metastases in both study II and IV and contrasted the findings for pulmonary metastases. Potential mechanisms could be age-related changes in lymphatic flow, decline in immunological function and alterations in mutational status [128]. Age per se is most likely not a true risk factor. The association between age and pulmonary metastases could simply be explained by a more advanced tumour stage in elderly at diagnosis and the association disappeared in study IV after the adjustment for relevant pathological features of the index cancer including T- and N-stage. Nevertheless, pulmonary metastases do occur even in early tumour stages of the CRC [26].

In study IV it was investigated whether some of these differences could be associated with findings at the pathological staging, especially focusing on the significance of MMR. Previously, biomarkers have been associated with distant recurrence at specific sites. Such biomarkers could therefore potentially be used in a biomarker panel for elucidation of the clinical significance of IPN as seen in lung cancer screening [129]. KRAS mutation has been associated with pulmonary but not liver relapse [130] and BRAF mutant tumours are associated with higher rates of peritoneal metastases, distant lymph node metastases, and lower rates of lung metastases [131]. Furthermore, a reduced risk of metastatic disease has been reported in patients with CRC and deficient MMR [131-134]. The investigation of MMR as a prognostic biomarker in the current setting and in relation to organ-specific metastases was chosen for obvious reasons; MMR status has been analysed routinely since 2010 and is in addition to a reduced overall risk of metastases known to be associated with gender, age, location of the index tumour, lymph node metastasis, cell type and degree of differentiation of the CRC [131,132,134]. However, despite the large-scale nationwide data used, the reduced risk of synchronous metastasis in dMMR tumours only applied to patients with hepatic metastases, whereas no statistically significant impact was found for pulmonary metastases. The rationale for this distinct pattern of metastatic spread, associated by MMR status, is obscure. Unfortunately, based on the present results MMR status adds no value in the assessment of IPNs.

**CONCLUSION**

Pulmonary metastases were confirmed to be the most common extra-hepatic manifestation for synchronous metastatic disease in patients with CRC. The optimal approach to the initial staging with regard to SPCM is debated. An increasing number of SPCM were detected with the implementation of chest CT in staging, however, a substantial and varying number of pulmonary lesions detected at chest CT could not readily be classified as being or

malignant. In study I and III we assessed the prevalence of IPN and specific radiological and/or clinicopathological factors associated with malignancy of IPN in previous published studies and in a local cohort. In previously published series, an average of 9% of all patients with CRC and staged with chest CT had IPN. However, the number of detected IPNs varied greatly between the studies and definitions of IPN differed if they were given at all. One in 100 of all chest CT staged patients had an IPN that ultimately proved to be malignant. Most pulmonary nodules were of benign origin and the few IPNs proving to be malignant were without pathognomonic features. In our local cohort the number of IPNs registered in the primary chest CT review was comparable to the average number from previous studies.

However, the number of IPNs was significantly reduced when scans were re-assessed by a dedicated thoracic radiologist. Unfortunately, neither in study III we found any radiological features of IPNs pathognomonic for malignancy and time to resection of the primary tumour was prolonged in patients with IPN.

SPCM were detected in 7.5% of all newly diagnosed CRC patients in study II, and their presence significantly impaired survival. Resection of the metastases and index tumour in addition to chemotherapy was associated with a prolonged overall survival, though only few patients were subjected to all three treatment measures. Based on the prevalence of SPCM, their impact on survival and potential benefit of early diagnosis and treatment we recommend that IPN should be followed-up in a systematic and pre-defined way. The total number of IPNs can be reduced by a review of dedicated thoracic radiologists and the remaining IPNs after such a review should be allocated to further investigations as suggested. Of outermost importance is that this further follow-up does not delay treatment of the index cancer. In the future, biomarkers for pulmonary metastases could potentially be implemented in the management strategies of IPN. In study IV MMR did, however, not prove to be of any value in evaluation of the risk of SPCM.

## PERSPECTIVES FOR FUTURE RESEARCH

Even as this thesis is being written the techniques used for staging, their applicability and the understanding of the metastatic process are rapidly evolving. It has been argued that cancer treatment, in developed countries, is becoming a culture of excess characterized by over-diagnosing, overtreatment and over-promising [135]. As a result, global economic expenditure on cancer care is increasing [135]. The expenses for the implementation of new and evolving diagnostic imaging modalities are no exception [136]. Future research and introduction of new (and potentially more expensive) staging modalities need to take the cost-effectiveness aspect into account. In this context future prospective studies should seek to clarify the "oncological benefit" from following IPNs and the concurrent consequences including increased radiation and patient anxiety. Some sceptics argue that the potential harmful effects of follow-up outweigh the potential benefit, which is why patients with IPN should not be subjected to any further diagnostic work-up; most of them prove to be benign anyway and the effectiveness of pulmonary metastasectomy is still to be resolved. However, as stated by MacMahon et al., [43] it is impossible to ignore the medicolegal considerations when discussing management of IPN and the nodules cannot simply be ignored because some of them do represent metastatic disease. A key component in future research should be

that reproducible and objective patient and nodule characteristics dictate the further work-up and treatment. Thereby ensuring a very selective use of surgery almost reserved for malignant nodules. Future predictive model could include biomarkers similar to plasma biomarker panels for discerning clinical significance of IPN as seen in non-small cell lung cancer [129]. The translation of biomarkers and increasing knowledge on determinants for the metastatic process into the clinical decision-making could be relevant for both patient and society cost benefit.

## SUMMARY

Patients with newly diagnosed colorectal cancer (CRC) are subjected to a preoperative thoraco-abdominal CT scan to determine the cancer stage. This staging is of relevance with regard to treatment and prognosis. About 20% of the patients have distant metastatic spread at the time of diagnosis, i.e. synchronous metastases. Most common are hepatic metastases followed by pulmonary involvement.

The optimal staging modality for detecting synchronous pulmonary metastases is debated. It has been argued, that synchronous pulmonary metastases (SPCM) are rare in CRC and that the consequence of detecting SPCM is minimal.

Furthermore, the current staging practice is complicated by a high number of incidental findings on the thoracic CT, so-called indeterminate pulmonary nodules (IPN). IPN can potentially represent SPCM.

The purpose of this thesis was to estimate the prevalence, characteristics and clinical significance of IPN and SPCM detected at the primary staging in CRC.

Study I was a systematic review of published studies on IPN in CRC focusing on the prevalence and radiological characteristics of IPN proving to be malignant. This knowledge would be of value in management strategies for IPN. On average 9% of all patients staged with a thoracic CT had IPN, however, the prevalence varied significantly between patients series. This was mainly attributed to varying/lacking definitions on IPN and variable radiological expertise in the assessment of the scans. Data were too inconsistently reported in the case series for a robust statement to be made on potential radiological characteristics suggestive of malignancy in IPN. Lymph node metastasis was the most common clinicopathological finding associated with malignancy of IPN. In conclusion, 1 patient of every 100 scanned patients had an IPN proving to a SPCM at follow-up, but we found no evidence that IPN should result in intensified diagnostic work-up besides routine follow-up for CRC.

Study II was an analysis of the prevalence of and risk factors for SPCM in a Danish nationwide cohort of patients with newly diagnosed CRC from 2001 to 2011. SPCM were detected in 7.5% of the patients and in 37% of these cases the metastatic spread was confined to the lungs. The prevalence of SPCM increased with the implementation of thoracic CT in CRC staging. SPCM impaired survival significantly and was associated with increasing age and rectal cancer. Resection of the primary tumour, resection of the SPCM and treatment with chemotherapy were associated with improved survival. Unfortunately, however, only very few patients were subjected to all three treatment measures, and the improved prognosis could simply be the result of a selection bias.

The inter-observer variation in classification of findings at thoracic CT scans was investigated in study III and was based on staging CT scans from a local cohort of patients with newly diag-

nosed CRC. Based on an experienced thoracic radiologist's assessment of the scans, we searched for radiological characteristics of IPN that could predict malignancy of the nodule. There was a significant difference in the number of IPNs detected between the primary and the thoracic radiologist's assessment. The thoracic radiologist classified fewer nodules as IPN and even reported with higher specificity and sensitivity for SPCM. More than 20% of IPNs (as classified by the thoracic radiologist) proved to be SPCM. Unfortunately, no radiological characteristics could be associated with a malignant outcome. In continuation of these findings we suggested a secondary review of scans with IPN be a group of dedicated thoracic radiologists. This approach might reduce the need for additional work-up for IPN and calls for clarification in future prospective studies. Identification of patients in particular risk of SPCM could be of value in the assessment of pulmonary nodules. Several biomarkers have been proposed for differential metastatic patterns in CRC.

In study IV we investigated the significance of mismatch repair status (MMR) for the location of metastatic spread in a nationwide Danish cohort of patients with newly diagnosed CRC between 2010 and 2012. Deficient MMR was associated with a reduced risk of synchronous metastatic disease, however, the risk reduction only applied to hepatic metastases. MMR had no impact on SPCM and is therefore currently of no use in the assessment of IPN.

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