Imaging Related To

Transplantation For Colorectal Liver Metastases

HARALD GRUT

DEPARTMENT OF RADIOLOGY AND NUCLEAR MEDICINE
OSLO UNIVERSITY HOSPITAL

INSTITUTE OF CLINICAL MEDICINE
FACULTY OF MEDICINE
UNIVERSITY OF OSLO

NORWAY

2018

Oslo University Hospital

UiO : University of Oslo

© Harald Grut, 2019

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-405-4

All rights reserved. No part of this publication may be
reproduced or transmitted, in any form or by any means, without permission.

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

“Intelligence is the ability to adapt to change.”

STEPHEN HAWKING

English physicist (1944–2018)

TABLE OF CONTENTS

ACKNOWLEDGEMENTS...……07
ABBREVIATIONS ……..……...…. 08
LIST OF PAPERS ……..……...…. 10
1. INTRODUCTION……..11
1.1 Colorectal cancer…… 11
1.1.1 Epidemiology……...11
1.1.2 Etiology……..... 11
1.1.3 Pathology……...……..……12
1.1.4 Imaging……...……..... 12
1.1.4.1 CT……...……..…….....13
1.1.4.2 MRI……14
1.1.4.3 Ultrasound……..…15
1.1.4.4 ^{18}F–FDG PET/CT ……..…… 16
1.1.4.5 Follow–up……..23
1.1.5 Treatment……..……..... 24
1.1.5.1 Primary tumor……..……..24
1.1.5.2 Liver metastases……..... 25
1.1.5.3 Pulmonary metastases……..…27
1.2 Liver transplantation for malignant disease …….…. 28
1.3 The secondary cancer (SECA) study…… 28
1.3.1 Background……..28
1.3.1.1 Improved surgical technique……..29
1.3.1.2 New immunosuppressing drugs …….…… 29
1.3.1.3 Improved preoperative imaging ……...……... 31
1.3.1.4 Availability of liver grafts……..…….. 32
1.3.2 Study logistics……...……32
1.3.3 Inclusion criteria……..33
1.3.4 Exclusion criteria……33
1.3.5 Immunosuppression protocol……..……..……..…….....34
1.3.6 Clinical outcome……..……... 34

2. AIMS…….....36
3. SUMMARY OF PAPERS……37
4. DISCUSSION ……..…… 40
4.1 Material and methods……..……...41
4.2 Statistical analysis…….. 48
4.3 Ethics…….. 49
4.4 Discussion of results……..……..... 50
Paper I: Growth rates of pulmonary metastases……..…...50
Paper II/III: ^{18}F–FDG PET/CT as prognostic tool and in patient selection.. 53
5. CONCLUSIONS……...56
6. FUTURE PERSPECTIVES……..…….…….…… 57
6.1 Clinical perspectives……..…… 57
6.2 Imaging perspectives (PET)…….……..…….. 60
6.2.1 Improved PET technology……60
6.2.2 New PET tracers…….……62
6.2.3 Dynamic PET. ……..……63
6.2.4 Texture analysis……..63
6.2.5 Final message……64
7. REFERENCES……..… 65
8. PAPERS……87

ACKNOWLEDGEMENTS

This work was performed from January 2016 to October 2018 and was supported by the Department of Radiology and Nuclear Medicine at Oslo University Hospital.

First, I would like to thank my main supervisor, Dr. Svein Dueland, for giving me the opportunity to work on the SECA study. His experience and enthusiasm for the SECA study and research has inspired me throughout this work. He has been present and available whenever I needed support seven days a week.

I am grateful to my co–supervisor Associate Professor Mona Elisabeth Revheim for her inspiring approach to research and for giving me time off to work on this thesis. Thanks for interesting discussions about all kinds of research related issues.

Thanks to my co–supervisor Professor Pål–Dag Line who was one of the initiators of the SECA study. I have appreciated his positive and pragmatic approach. His experience in the field of transplantation and perspectives has definitely strengthened the thesis.

Thanks to all my co-authors; PhD Therese Seierstad, Associate Professor Steinar Solberg, MD Tor S. Egge and Dr. Stein Gunnar Larsen for their valuable contributions.

A special thanks to my parents Oddveig and Helge who have followed me through my education with their support and care.

Finally, I would like to thank my wife Kjersti for her support and understanding. And the most important, our two inspiring and beautiful girls Marlene (3) and Marie (6).

Harald

ABBREVIATIONS

AUC	Area under curve
BRAF	V–raf murine sarcoma viral oncogene homolog B1
CEA	Carcinoembryonic antigen
CECT	Contrast enhanced computed tomography
CEUS	Contrast enhanced ultrasound
CLM	Colorectal liver metastases
CNI	Calcineurin inhibitors
CRC	Colorectal cancer
CT	Computed tomography
DFS	Disease free survival
DPET	Dynamic positron emission tomography
DT	Tumor volume doubling time
ECD	Extended criteria donors
ECOG	Eastern cooperative cancer group (performance status)
EGFR	Epidermal growth factor receptor
ELTR	European Liver Transplant Registry
^{18}F	Fluorine–18
FDG	Fluorodeoxyglucose
HK	Hexokinase
HU	Houndsfield unit
KRAS	Kirsten rat sarcoma
LN	Lymph node
LT	Liver transplantation
MBq	Mega becquerel (radioactivity)
MRI	Magnetic resonance imaging
MDT	Multidisciplinary team
MTV	Metabolic tumor volume
NCLM	Nonresectable colorectal liver metastases
NLTR	Nordic Liver Transplant Registry
NRAS	Neuroblastoma–RAS
OS	Overall survival

OUH	Oslo University Hospital
PET	Positron emission tomography
PMI	Per million inhabitants
PSF	Point–spread–function
PERCIST	Positron emission tomography (PET) response criteria in solid tumors
RECIST	Response criteria in solid tumors
RFA	Radiofrequency ablation
ROC	Receiver operating characteristic (curve/analysis)
ROI	Region of interest
SBRT	Stereotactic body radiation therapy
SECA	Secondary cancer
SIRT	Selective internal radiation treatment
SNR	Signal–to–noise ratio
SUV	Standardized uptake value
TACE	Transarterial chemoembolization
T/B–ratio	Tumor to background ratio
TOF	Time–of–flight
TLG	Total lesion glycolysis
TME	Total mesorectal excision
TNM	Tumor, lymph node, metastases (staging)
US	Ultrasound
VOI	Volume of interest

LIST OF PAPERS

I **Grut H**, Solberg S, Seierstad T, Revheim ME, Egge TS, Larsen SG, Line PD, Dueland S. Growth Rates of Pulmonary Metastases after Liver Transplantation for Unresectable Colorectal Liver Metastases. **British Journal of Surgery**. 2018 Feb;105(3):295–301

II **Grut H**, Dueland S, Line PD, Revheim ME. The Prognostic Value of ^{18}F–FDG PET/CT Prior to Liver Transplantation for Nonresectable Colorectal Liver Metastases. **European Journal of Nuclear Medicine and Molecular Imaging**. 2018 Feb;45(2):218–225

III **Grut H**, Revheim ME, Line PD, Dueland S. Importance of ^{18}F–FDG PET/CT to Select Patients with Nonresectable Colorectal Liver Metastases for Liver Transplantation. **Nuclear Medicine Communications.** 2018 Jul;39(7):621-627

1. INTRODUCTION

1.1 Colorectal cancer

1.1.1 Epidemiology

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women, making CRC one of the leading causes of cancer–related morbidity and death (1). The incidence of CRC was 4343 in Norway in 2016, and the median age at diagnosis is about 70 years. Norway has higher incidence of CRC than other European countries and the United States. The last 60 years a significant increase in incidence has been registered and this is expected to continue the next decade, mainly due to the aging population. Five–year survival is currently about 60% for colon cancer and 66% for rectal cancer. In the 1960s the 5–year survival was less than 30% (*Figure 1*) (2).

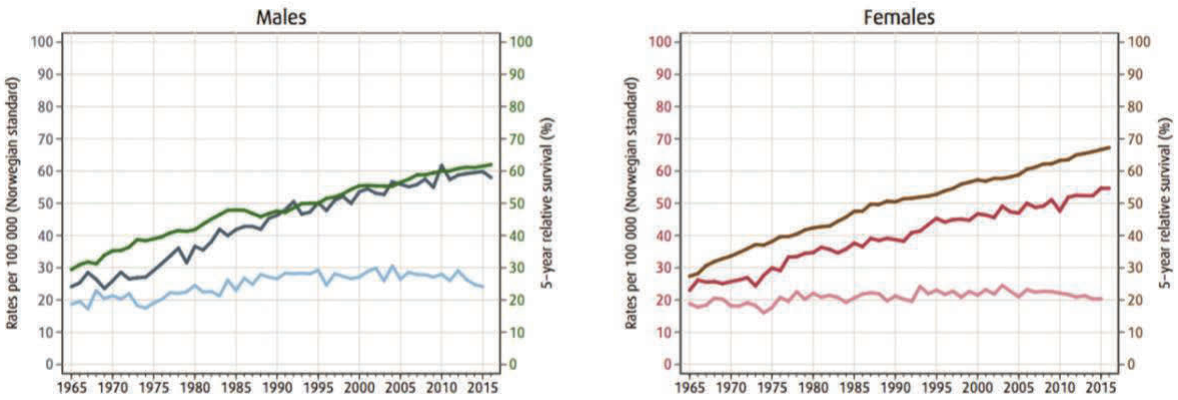

Figure 1: *Development of incidence (dark blue and red line), survival (green and brown line) and mortality (bright blue and pink line) of colon cancer the last 50 years in Norway for males and females. Re-printed with permission from the Norwegian cancer registry (2).*

1.1.2 Etiology

Development of CRC is a multifactorial interaction between genetic and environmental factors. Age and familial history are the most common risk factors. There is a 2 to 3–fold increased risk of developing CRC in people who have one first–degree relative and the risk is even higher if the cancer developed at a young age (<45 years). There is a 3 to 4–fold increased risk of CRC who have two first degree relatives (3). It is suggested an inverse relation between fiber intake and CRC risk and that physical activity decreases the risk of CRC (4). The risk of both colon and

rectal cancer is increased by red and processed meat, alcohol and obesity (5, 6). Familial adenomatous polyposis and Lynch syndrome (Hereditary Non–Polyposis Colorectal Cancer) are well known genetic familial cancer syndromes accounting for 5–6 % of the CRCs (7). Pancolitis in ulcerative colitis and Crohn disease confers a 5 to 15–fold increased CRC risk compared to the general population (8-11).

1.1.3 Pathology

More than 90% of all CRCs are adenocarcinomas arising from dysplastic adenomatous polyps from epithelial cells of the colorectal mucosa. The transformation from normal columnar epithelium to invasive cancer includes inactivation of tumor–suppressor and DNA repair genes and activation of oncogenes (12, 13). About 70% of the adenocarcinomas are moderately differentiated, 20% are highly differentiated and 10% poorly differentiated (13). Other rare histologic types are neuroendocrine neoplasms, mesenchymal tumors and lymphomas (14).

Molecular and genetic analyses are increasingly used in the characterization of CRC (15). Certain molecular biomarkers can predict clinical outcome beyond conventional staging and improve selection of patients to targeted biological agents or immunotherapy (16). Epidermal growth factor receptor (EGFR) and its signaling pathways are involved in the development and progression of many cancers, including CRC. KRAS/NRAS (Kirsten rat sarcoma/Neuroblastoma–RAS), and BRAF (v–raf murine sarcoma viral oncogene homolog B1) are components of the EGFR signaling pathway. Mutations of these genes are found in approximately 40% and 10% of the CRC patients and cause resistance to anti–EGFR therapy (13, 17-19). Thus, mutation analysis is important to select the patients who will benefit from this treatment.

1.1.4 Imaging

Development and improvement of the different imaging modalities the two last decades is one of the reasons for the improved survival observed in CRC patients. Modern imaging techniques makes us able to tailor and optimize the primary treatment and treatment of recurrent disease (20-24).

1.1.4.1 Computed tomography

Computed tomography (CT) is a diagnostic imaging technique using x–rays to make cross–sectional images of the body. The density of the tissue passed by the x–ray beam can be measured from the calculation of the attenuation coefficient. The attenuation coefficients are converted to Houndsfield units (HU). HUs range from –1000 to 1000 where –1000 represents air, 0 water and 1000 cortical bone. Soft tissue typically ranges from 30–80 HU. Based on the HU, cross-sectional images for axial, sagittal and coronal view and assessment can be made. Usually, iodine containing contrast agents are injected intravenously prior to the CT scan to enhance the contrast between different soft tissues making a contrast enhanced CT (CECT). Last generations CT scanners generate high resolution images of large body volumes within a few seconds (25).

CECT of thorax, abdomen and pelvis is the workhorse in CRC imaging and is used in the initial TNM staging of colon cancer, M staging of rectal cancer, follow–up and in the case of recurrent disease. Also, CECT is an important part of the planning of surgery considering organ topography and mapping of relevant vessel anatomy.

Colonoscopy or rectoscopy with biopsy is the primary method for diagnosing CRC. Histological diagnosis and correct TMN staging are important to make a proper treatment plan for each patient. If a cancer is detected at either rectoscopy or sigmoidoscopy a full colonoscopy should be performed either pre– or postoperatively because synchronous tumors are found in approximately 3.5% of the patients (26). If the endoscopy is incomplete, a CT colonography (virtual colonoscopy) can be performed to visualize the colon/rectum oral to the tumor and to detect significant polyps to choose a proper surgical strategy. CT colonography can be the primary diagnostic method in patients more than 75 years with low performance status or in comorbid patients.

CECT is used for both T and N staging in colon cancer. T–status is an important prognostic factor and CECT can distinguish T1/T2 from T3/T4 tumors (27). The assessment of lymph nodes (LNs) by CECT is difficult and size criteria have a sensitivity and specificity of only 70 and 78% (28).

CECT is a sensitive modality to detect distant CRC metastases (M status). Liver and pulmonary metastases are the most common metastatic sites and the follow–up program is specially focused on these organs (29). However, other sites like peritoneum, omentum, other organs and the skeleton are also assessed.

Hypodense liver lesions are frequently detected by CECT. Is it important to decide if these lesions are malignant or benign. Solitary lesions can be assessed further by contrast enhanced ultrasound if the acoustic conditions for the ultrasound are acceptable. If several lesions are found, or the lesions are small (<10mm), MRI with diffusion sequences and hepatocyte specific contrast agents are recommended (30).

CT has a high sensitivity for detecting pulmonary metastases. Even though the specificity can be low (20-74%), this serves as an important baseline for subsequent follow–up CT examinations (31).

1.1.4.2 Magnetic resonance imaging

Magnetic resonance imaging (MRI) uses the magnetic properties of the hydrogen protons in the body. When placing a patient inside an MRI machine the protons align to the strong magnetic field. During imaging radio frequency pulses are used to force the magnetism out of alignment (e.g. 90 degrees) with the strong static magnetic field of the MRI machine. As the energy from the radio frequency pulse dissipates the protons will return in alignment with the static magnetic field. This regain of magnetism with the static magnetic field is called T1 relaxation and loss of magnetism in the tissue (axial plane) is called T2 relaxation. T1 and T2 relaxation is the basis of MRI imaging and utilizes the differences between different tissues to create high resolution images. Gadolinium is paramagnetic and can be used as intravenous contrast agent in MRI. Gadolinium shorten T1 relaxation of voxels where it is present resulting in brighter signal in T1 weighted images. Hepatocyte specific gadolinium contrast agents are utilized to characterize liver lesions. Diffusion weighted images (DWI) are made on the basis of the motion of water molecules within a volume of tissue (voxel). High cellular tissues as seen in many malignant tumors or cellular swelling as seen in stroke can restrict the movement of water and be seen as high signal MRI lesions (32).

Due to the high resolution, diffusion sequences and contrast agents, pelvic MRI is used in the initial T and N staging of rectal cancer, but also in the response evaluation following radio chemotherapy (33). The main goal is to identify patients with increased risk of metastatic disease; patients with short distance (<2mm) to or growth through the mesorectal fascia, tumor located to the inferior part of rectum, extramural tumor depth >5mm, extramural vein invasion, mucinous tumors, LN metastases or affection of the peritoneal fascia (33).

Accurate localization of the tumor (T stage) is important to determine the surgical technique and prognosis. Tumor located distal in the rectum have increased risk of recurrence (34). MRI can accurately determine the distance between the inferior part of the tumor and the puborectal muscle. Due to difficulties in distinguishing inflammation/fibrotic tissue from minimal tumor growth through the bowel wall, diagnosing T2 versus T3 can be challenging. In cases of deeper invasion through the bowel wall, MRI is more accurate (24). Some rectal cancers contain mucus and tumors with >50% mucus have poor prognosis. MRI has proved to be highly accurate in determining the amount of mucus in rectal cancers (35).

Like in CECT, the assessment of LNs (N stage) in MRI is challenging. The use of size criteria is uncertain and morphological assessment has been proven to be more accurate (36, 37). Usually the LNs are put into one of three categories; malignant, equivocal or benign. Due to the uncertainty in the assessment, equivocal mesorectal LNs should not be determining in the final choice of treatment (38).

Multiple, equivocal or small (<10mm) indeterminate liver lesions are often found on CEUS. MRI has higher spatial resolution than CT, and by utilizing diffusion sequences and hepatocyte specific contrast agents, usually these lesions are diagnosed by a supplementary MRI of the liver (30).

1.1.4.3 Ultrasound

Ultrasound (US) uses high–frequency sound waves to characterize different tissues. US transducers (probes) send US waves into the tissue and receive an echo. Based on this echo, grey tone images are made. In contrast enhanced US (CEUS) intravenous contrast agents containing microbubbles are administered. The

microbubbles enhance vascular structures contrast like the contrasts agents used in CT and MRI (39).

In the primary staging of CRC, US and CEUS is utilized in patients with contraindications to CT and MRI contrast like renal failure and contrast allergy. CEUS of the liver is an integrate part of the follow–up after primary surgery (40).

Rectal endoscopic ultrasound is the best modality to distinguish premalignant from malignant tumors and the staging of T1 versus T2 tumors (41-43). The method is also better than MRI to determine if the sphincter muscles are affected in distal rectal cancers. Also, US is used to guide cytology sampling and biopsies of suspected soft tissue metastases.

1.1.4.4 ^{18}F–FDG PET/CT

F–18 fluorodeoxyglucose positron emission tomography in combination with CT (^{18}F–FDG PET/CT) combines anatomic information from CT and metabolic information from ^{18}F–FDG (44). ^{18}F–FDG PET/CT is utilized for initial diagnosis, staging, restaging, assessment of treatment response and prognosis in multiple cancers. In addition, the method can contribute significantly in assessment of equivocal findings from other imaging modalities (45). FDG is a glucose analogue and ^{18}F is a cyclotron made positron emitting radioactive isotope with half time of 110 minutes. ^{18}F–FDG is injected prior to the PET/CT scan and ^{18}F–FDG is taken up by glucose consuming cells through the glucose transporters (GLUTs) in the cell membrane like regular glucose. In the cell cytoplasm, FDG undergoes phosphorylation to form FDG–6–phosphate (6P) by hexokinase (*Figure 2*). In contrast to regular glucose, FDG–6P cannot undergo further metabolism and becomes trapped inside the cell. Increased glucose utilization in malignant cells is explained by the up–regulation of hexokinase activity (44).

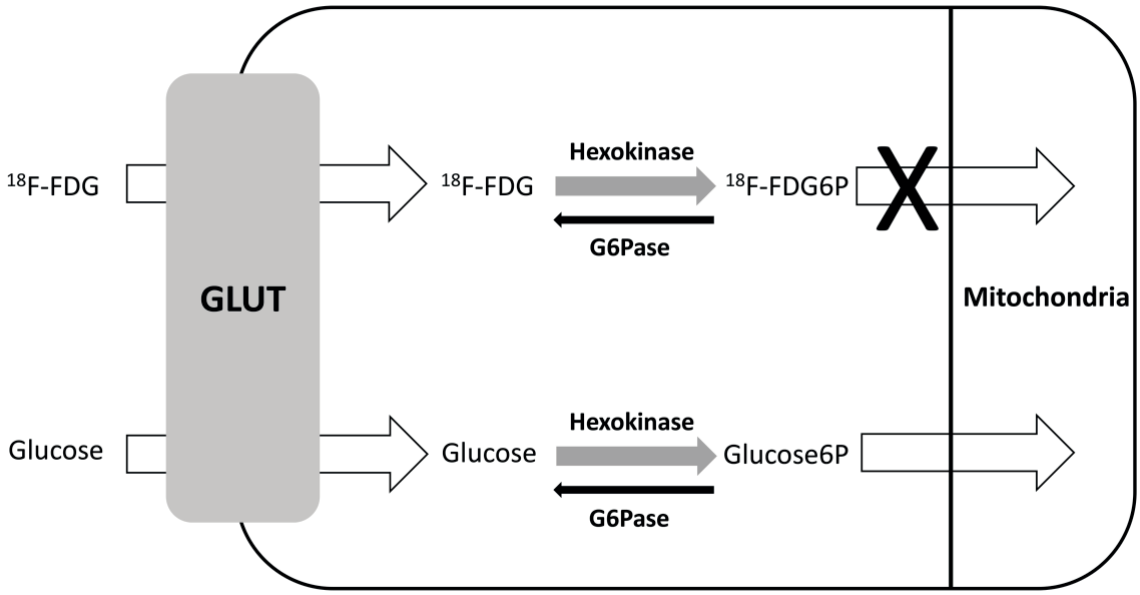

Figure 2: Metabolization of ^{18}F–FDG. *The figure illustrates how ^{18}F–FDG is taken up into a cell by the glucose transporter (GLUT) and phosphorylated by hexokinase but cannot undergo further metabolization and becomes trapped inside the cell unlike regular glucose.*

Positrons emitted from ^{18}F interacts with atoms in the surrounding tissue. When the kinetic energy is about zero, the positron annihilates with an electron forming two photons moving in opposite direction (180° ± 0.5°) with an energy of 511 keV. The detection of annihilated photons along this line–of–response is the basis of PET imaging and is used to localize where the annihilation reaction actually occurred inside the patient (*Figure 3*). Small crystal scintillation detectors inside the PET scanners detect the photons to build an image (46).

The FDG accumulation in tumors and other tissue is usually quantified by standardized uptake values (SUVs). PET scanners measure the in vivo radioactivity concentration (kBq/ml) being directly linked to the FDG concentration. This measured radioactivity is corrected for variations in administered activity (kBq) and body weight (g) for individual patients. The basic SUV expression is:

$$\mathbf{SUV} = \frac{\text{Measured radioactivity } (\frac{\text{kBq}}{\text{ml}})}{\frac{\text{Administered activity (kBq)}}{\text{body weight (g)}}}$$

Based on this, different SUVs can be utilized in measuring tumor activity. SUV_{max} is the pixel with the highest uptake in region of interest (ROI). SUV_{mean} is the mean SUV in a ROI and SUV_{peak} is defined as the SUV_{mean} of the volume of 1 cm^3 around the SUV_{max}. If the injected FDG is homogenously distributed in the body, the SUV will be 1 g/ml everywhere for any injected activity or body weight. All SUVs are under the assumption that 1ml equals 1g of tissue (44, 47, 48).

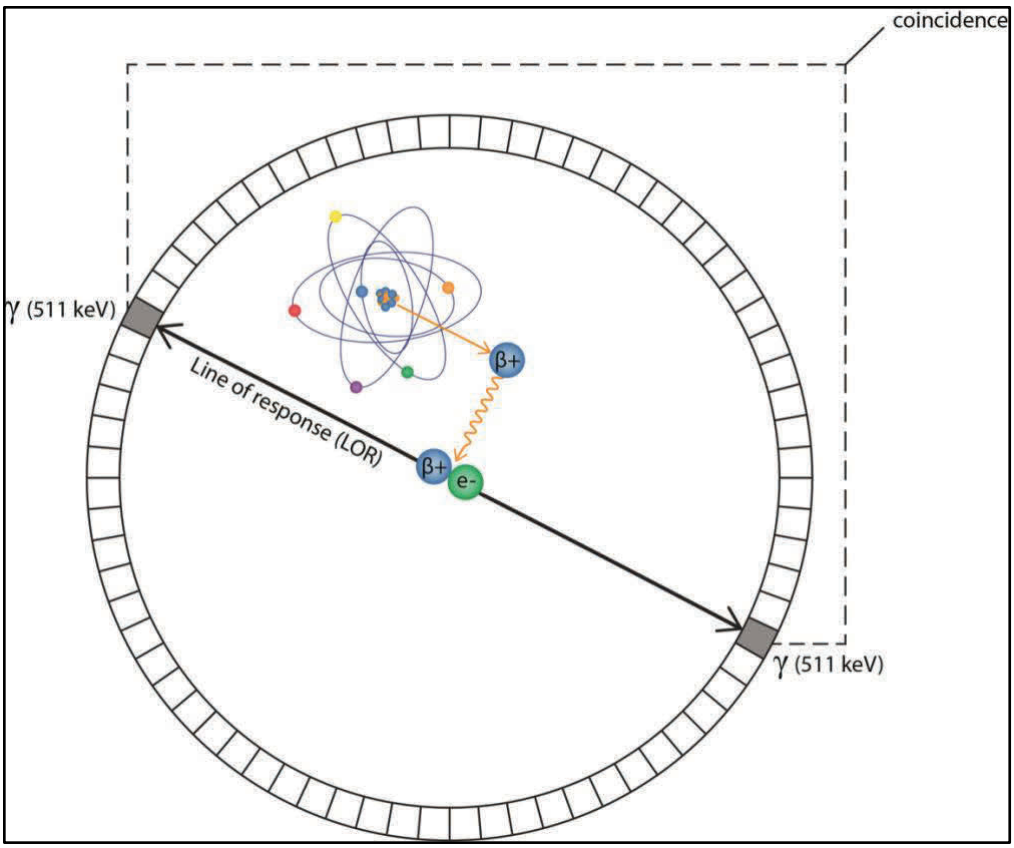

Figure 3: PET principle. *The basis of PET imaging is the annihilation reaction by an electron (e-) and a positron (β+) from the decay of positron emitting radioisotope. By this reaction two photons (γ) are emitted with an energy of 511 keV in opposite direction (~180°) along the line of response and can be detected by the PET scanner.*

Metabolic tumor volume (MTV, cm^3) is defined as the tumor volume with ^{18}F–FDG uptake segmented by a certain percentage, for example a fixed threshold of 40%, of the SUV_{max} in a volume of interest (VOI). *Figure 4* shows an example of placing of a VOI around a large liver metastasis. Total lesion glycolysis (TLG, g) is calculated by multiplying SUV_{mean} by the MTV. Tumor to background (T/B) ratio is defined as SUV_{max} divided by liver background. According to the PET response criteria in solid tumor (PERCIST criteria) it is recommended to measure liver background by placing a ROI of 3 cm in the right liver lobe (49).

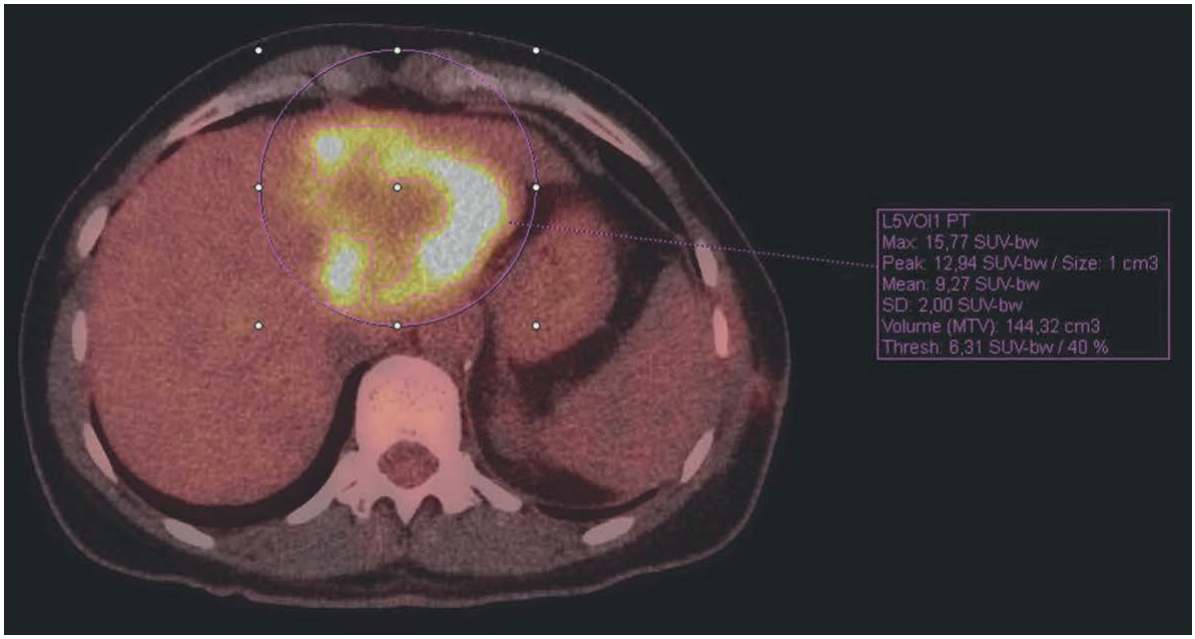

Figure 4: *Example of PET derived values (SUV_{max}, SUV_{peak}, SUV_{mean} and MTV) obtained by using Siemens syngovia software in a patient with a large metastasis in the left liver lobe.*

Primary diagnosis and staging

The American National Comprehensive Cancer Network (NCCN, Version 3.2017) on CRC does not recommend ^{18}F–FDG PET/CT in the general initial staging or as baseline modality in CRC (50). However, several studies are reporting high sensitivity (95–100%) in detecting primary tumors on ^{18}F–FDG PET/CT *(51-53)*. Only a few small studies have evaluated the possible benefit of ^{18}F–FDG PET/CT in the general initial staging of CRC (54-60). There is a lack of large uniform prospective studies. A systematic review by Virens *et al.* reported a mean change in the management of

10.7% and a higher impact in patients with high metastatic potential (60). Based on a study of 146 patients, Pelosi *et al.* are suggesting ^{18}F–FDG PET/CT in the primary diagnosis and staging of rectal cancer compared to conventional imaging techniques (61).

Overall, ^{18}F–FDG PET/CT is considered to be *potentially useful* but still not routinely recommended in the presurgical initial staging of CRC (50, 61). However, ^{18}F–FDG PET/CT should be used to evaluate equivocal findings from CECT or MRI if this information will change management, or in patients with contraindications to intravenous CT contrast (50).

Restaging of local recurrence and metastases

An expert panel consisting of twelve American and European experts recently (2017) evaluated the appropriateness of ^{18}F–FDG PET/CT in the restaging of local recurrence and metastases and in assessment of treatment response in CRC (45). The panel concludes that most patients with suspected local recurrence or metastases present with either local symptoms, findings on anatomic imaging (CECT/MRI) or other nonspecific indications like rising carcinoembryonic antigen (CEA), and that the next step will be another imaging modality like ^{18}F–FDG PET/CT.

The sensitivity of ^{18}F–FDG PET/CT to detect local recurrence is reported to be 94% in several studies and the specificity ranges from 93%–98% (62-65). The panel believes that ^{18}F–FDG PET/CT is *appropriate* in suspected local recurrence given the high reported sensitivity and specificity (45).

Unlike local recurrence, metastases are to be located distant from the primary tumor. The most common sites for CRC metastases are the liver and the lungs. Several studies have evaluated PET/CT in comparison with CECT and MRI for the detection for liver metastases. A meta–analysis from 2010 including 39 articles and 3391 patients reported a mean per–patient sensitivity and specificity of 84%/95% for CECT, 88%/92% for MRI and 94%/96% for PET. Per–lesion sensitivities were 74%, 80% and 81%, respectively (66). In another metaanalysis from 2010 including 25 studies Floriani *et al* reported sensitivity and specificity of 63%/98% for ultrasound, 75%/96% for CECT, 81%/97% for MRI and 94%/99% for PET (67). In a more recent

meta–analysis including 18 studies of patients with known or suspected liver metastases Maffione *et al* report a per–patient sensitivity for PET of 93%, CECT 100% and MRI 98% and on a lesion basis the corresponding values were 66%, 89% and 79%. However, PET appeared to be more specific than CECT and MRI (86%, 81% and 67%). I addition, PET changed patient management by detecting extrahepatic disease in 24% of the patients (68). Only a few articles have assessed extrahepatic metastases outside the local tumor site. A meta–analysis from 2005 reports a pooled sensitivity and specificity for extrahepatic metastases of 92%/95% compared with 61%/91% for CECT (69). Another meta–analysis from 2009 reported a pooled sensitivity and specificity for distant metastases of 91%/83% (65).

The expert panel concludes that ^{18}F–FDG PET/CT is *appropriate* for assessment of extrahepatic abdominopelvic metastases and the evaluation of suspected metastases after negative or equivocal findings on anatomic imaging (CECT or MRI), especially in the case of rising CEA (45). The American NCCN concerning CRC state that ^{18}F–FDG PET/CT *should be considered* in the case of increasing CEA with negative CECT/MRI and in the case of potentially curable metastasectomy. The purpose of this ^{18}F–FDG PET/CT is to identify unrecognized metastatic disease that would preclude the possibility of surgical management (68, 70).

According to the expert panel and NCCN, ^{18}F–FDG PET/CT is neither recommended in the general surveillance after primary surgery or the surveillance of metastases (45, 50, 71). A economic cost analysis concluded that ^{18}F–FDG PET/CT as an add–on modality is cost–effective in the preoperative staging of recurrent and metastatic CRC, but not in primary CRC (72).

Response of metastases during and after chemotherapy

Several studies have evaluated the PET response on metastases during and after chemotherapy and related different PET parameters to outcome. The expert panel state that these indications *may be appropriate* but should be restricted to patients who are candidates for further therapy or change of therapy depending on the result from the ^{18}F–FDG PET/CT imaging (45). It the case of inconclusive CT or MRI after ended chemotherapy, ^{18}F–FDG PET/CT was considered appropriate.

Assessment of neoadjuvant therapy for advanced rectal cancer

Due to mixed results in early studies, ^{18}F–FDG PET/CT has not been routinely used for this indication. Recent metaanalyses have shown more favorable results. Most of these studies identified a strong correlation between PET response (SUVs, MTV and TLG) and DFS and OS (73-76). However, there is no consensus whether this therapy assessment should be performed as an interim examination or after completed therapy. Also, only a few studies have compared ^{18}F–FDG PET/CT directly with other modalities. Three metaanalyses show similar accuracies as for MRI in the prediction of complete pathologic response (77-79). Another metaaanalysis showed that DWI from MRI was superior to ^{18}F–FDG PET/CT (80). Based on the current knowledge, the panel believes that ^{18}F–FDG PET/CT *may be appropriate* for this indication but should be reserved for those cases were clinical findings or other imaging studies raise questions regarding staging or patient management, especially if a baseline ^{18}F–FDG PET/CT is present (45). If metastases that would change patient management are suspected, ^{18}F–FDG PET/CT is considered to be *appropriate.* The current NCCN guidelines does not recommend ^{18}F–FDG PET/CT as a part of the regular assessment of neoadjuvant therapy for advanced rectal cancer, but state that "^{18}F–FDG PET/CT is being investigated for its ability to accurately determining response to neoadjuvant treatment" (50). The following table summarizes the appropriateness of 18F–FDG PET/CT in different CRC settings.

^{18}F–FDG PET/CT IN COLORECTAL CANCER	
Clinical setting	**Appropriateness**
General initial staging	May be appropriate[1]
Restaging for detection of local recurrence	Appropriate[2]
Restaging for detection of metastases	Appropriate[2]
Increasing CEA with negative or equivocal CT/MRI	Appropriate
Treatment response evaluation (chemo/radiation therapy)	May be appropriate
General surveillance	Not appropriate

[1] Recommended to assess equivocal findings from CT and/or MRI and in patients with contraindications to intravenous CT contrast.

[2] Especially recommended prior to potentially curative treatment/surgery.

1.1.4.5 Follow–up

The table shows the recommended imaging follow–up for patients undergoing intended curative treatment for CRC in Norway (40). Low dose chest CT and CEUS has replaced full dose (diagnostic) CECT the last decade to reduce the radiation dose to the patients.

RECOMMENDED IMAGING FOLLOW–UP IN COLORECTAL CANCER								
Modality	**Months after primary surgery**							
	6	12	18	24	30	36	48	60
CECT abdomen/pelvis[1]	X							X
CEUS liver[2]		X	X	X	X	X	X	
Low dose chest CT		X		X		X	X	X
Colon examination[3]								X

[1] CECT abdomen/pelvis includes an arterial phase scan of the liver and a portal venous phase scan of the abdomen and pelvis.

[2] In patients with profound liver steatosis or liver cirrhosis a portal venous phase CECT of the liver is recommended instead of CEUS.

[3] Colon examination at 60 months can be either colonoscopy or CT colonography.

1.1.5 Treatment

Optimal treatment is based on an accurate staging to choose the best treatment strategy. Choice of treatment is dependent of the TNM stage.

1.1.5.1 Primary tumor

Colon cancer

A complete mesocolic excision containing the primary tumor, LNs, lymphatic vessels and blood vessels is recommended (81-83). Although 5 cm is considered to be appropriate, most commonly the primary tumor is excised with 10 cm margin both orally and distally. Distal margin of 5 cm is sufficient in rectosigmoid cancers (84). The regional LNs are divided in local (N1), intermediate (N2) and central (N3) with corresponding terminology to name the extent of the LN dissection; D1, D2 and D3. In curative intended surgery a minimum of D2 dissection is recommended. Several studies have reported benefit by D3 compared to D2 dissection and consequently many hospitals perform D3 dissection routinely (81, 85-87). The extent of surgery is also determined by the local vessel anatomy and circulation of the bowel following LN dissection and vessel ligation (40).

Rectum cancer

Total mesorectal excision (TME) is the recommended surgical technique of rectal cancer (88, 89). Preoperative radiation therapy is given in primary resectable rectal cancers to reduce the risk of local recurrence (90-92). In locally advanced rectal cancer radiation therapy is given to downstage the tumor to achieve possible radical surgery. Improved results have been demonstrated by adding chemotherapy compared to radiation therapy alone (93, 94).

By TME the primary tumor including the lymphatic drainage is removed *in toto* by dissection along the mesorectal fascia. The dissection plane is based on an MRI examination performed prior to preoperative chemoradiation therapy (95). Sufficient resection margin is necessary to prevent local recurrence both in the circumferential and longitudinal plane. A three times increased risk of local recurrence is observed if the tumor or the tissue close to the tumor is perforated (96). In the upper part of the rectum a partial TME is considered to be sufficient, however a 5 cm margin of normal mesorectum distal to the tumor is recommended. By TME a distal margin of 1 cm is

accepted if this is necessary to establish an anastomosis. If the tumor grows into other organs or outside the mesorectal fascia an extended TME *en bloc* procedure is performed to possibly remove all tumor tissue.

1.1.5.2 Liver metastases

About half of the CRC patients develop metastases either at time of diagnosis or later on and the liver is the most frequent site. Approximately 15% have liver metastases at time of resection of the primary tumor (97). To optimize the treatment for each patient a multidisciplinary approach including surgeon, oncologist, radiologist and nuclear medicine physician is necessary (98).

Curative treatment

Liver resection is currently the only potentially curative treatment option for liver metastases with a 5–year survival reported to be 20%–58% depending of the clinopathological status of the patients and selection criteria (97, 99-102). However, only about 20% patients with colorectal liver metastases are candidates for curative liver resection. The preoperative imaging assessment of potentially resectable liver metastases includes CECT of thorax, abdomen and pelvis and MRI of the liver with hepatocyte specific contrast agents. CEUS is used to assess equivocal findings and ^{18}F–FDG PET/CT should be used to exclude extrahepatic metastases (103-105). Liver biopsy is not indicated unless resection is not possible or if the radiological diagnosis is uncertain. Biopsy can potentially give implantation metastases (40). In most cases the primary tumor is resected prior to liver resection. Also, there should be no signs of extrahepatic disease and the metastases have to be technically resectable with an adequate volume of the liver remnant. In selected cases where the liver metastases are considered to be the most advanced and prognosis limiting part of the CRC disease, the liver metastases are resected prior to the primary tumor (liver first strategy) (106). Even though there is a lack of scientific documentation and international consensus, preoperative neoadjuvant chemotherapy is usually given in patients with multiple liver metastases (40). Conversion chemotherapy is given to patients who potentially can convert from nonresectable colorectal liver metastases (NCLM) to resectable disease. This chemotherapy regimen usually consists of 5–fluororuracil (5–FU) and oxaliplatin or irinotecan, sometimes in combination with

monoclonal antibodies. Following this treatment, a new evaluation on resectability is performed.

Palliative treatment

The main goals of palliative treatment regiments are to improve survival, decrease symptoms and maintain quality of life (107). Median survival of untreated metastatic CRC is poor and reported to be only up to about 6–7 months (107-109). Chemotherapy is a palliative treatment modality of NCLM. First line chemotherapy is in most patients cytotoxic treatment consisting of 5–fluorouracil (5–FU)/calsiumfolinate in combination with oxaliplatin or irinotecan. In Norway these regimens are usually given as a bolus 5–fluororuracil (FLOX/FLIRI) in contrast to the international protocols where the 5–fluororuracil treatment is given as a 46–48 hour infusion (FOLFOX/FOLFIRI) (107, 110-112). When an EGFR inhibitor is added, a 10–20% increase in response rates in patients with RAS wild type tumors has been shown (19). Second line chemotherapy is given when progression of disease on first line is observed. If there is progression on first line irinotecan containing regimen, it is recommended to switch to an oxaliplatin containing protocol, and the other way around. The EGFR inhibitor (Cetuximab) in combination with irinotecan as third line treatment leads to a 4–5 months prolonged survival in patients with progression on 5–FU, oxaliplatin and irinotecan if they have not previously received EGFR inhibitor. Cetuximab or Panitumumab as monotherapy has shown improved response rates in RAS wild type tumors (113, 114). Median overall survival (OS) from start of first line chemotherapy is about 2 years and the 5–year OS is about 10%, although longer survival is observed in patients with good performance status (ECOG 0-1), no (K)RAS or BRAF mutations and left-sided tumors (115-119).

Other treatment options for NCLM:

- Radiofrequency ablation (RFA) destroys tumors by heat (120).
- Selective internal radiation treatment (SIRT) is a modality whereby radioactive labeled (Yttrium–90) microspheres are injected to the hepatic arterial blood supply of the metastases causing blocking of small arteries as well as radiation to destroy tumor cells. SIRT is also given to patients with NCLM or patients who have not responded to chemotherapy prior to planned liver surgery (121).

- Stereotactic body radiation therapy (SBRT). In selected cases radiation therapy in high, focused doses is used as a potential curative treatment, or to reduce tumor load (122).
- Transarterial chemoembolization (TACE). During this procedure a microcatheter is selectively placed in smaller hepatic arteries supplying the tumor for administration of combined chemotherapeutic drugs and embolic agent (123).

These therapies for NCLM are usually only palliative, although RFA and SBRT have curative potential. In some cases, the listed treatment options are used as downstaging prior to surgery or to possibly achieve resectability. To select the best possible treatment strategy for individual patients, these cases are therefor discussed in multidisciplinary teams.

1.1.5.3 Pulmonary metastases

About 10% of the patients undergoing surgery for CRC develop pulmonary metastases (124). No controlled studies have ever documented the effect of resection of pulmonary metastases from CRC. However, resection for selected patients with colorectal pulmonary metastases is an established treatment (125). The current criteria for pulmonary metastasectomy are based on those of Ehrenhaft and Thomford originally described 6 decades ago and include (126, 127):

1. The primary malignancy must be controlled or controllable.
2. There is no extrathoracic metastasis that is not controlled or controllable.
3. All of the tumor must be resectable, with adequate remaining pulmonary reserve.

In cases where surgery and SBRT are considered to be equal concerning outcome and complications, surgery is most often preferred. A systematic review reported a 5–year survival between 38% and 64% (median 53%) after pulmonary metastasectomy (128). Ten–year survival is about 30% (129). As for CRC liver metastases, a multidisciplinary approach is essential in the management of colorectal pulmonary metastases to achieve the best possible medical decisions and outcomes (130).

1.2 Liver transplantation for malignant disease

According to the European Liver Transplant Registry (ELTR) malignancy accounted for 16.5% of all LTs in the period 1988–2015. Hepatocellular carcinoma (HCC) is the main cancer indication for LT with 13.5% of all LTs in the Nordic Liver Transplant Registry (NLTR) in 2016. Also, some patients with hilar cholangiocarcinoma are treated with LT. According to the NLTR, the 5–year survival following LT for HCC and cholangiocarcinoma was 66% and 42% in the period from 2004 to 2013. For secondary malignancy, well differentiated neuroendocrine tumors (WHO grade 1/2, KI67 <10% recommended) have been recognized as a LT indication with a reported 5–year survival of about 60% (131-133).

Fifty cases of LT for NCLM have been registered in ELTR before 1995 with a 1– and 5–year OS of 62% and 18% (134, 135). About half of these patients died due to complications related to the LT procedure and other non–cancer related causes. In addition, the efficacy of the immunosuppressive regiments was lower and many centers had limited overall experience. Due to liver donor shortage and poor survival compared with other indications for LT, transplantation for NCLM was abandoned. Subsequently, only a few cases with long term survival have been reported (134, 136, 137).

1.3 The secondary cancer (SECA) study

1.3.1 Background

Standard care of patients with NCLM is chemotherapy with 5–year survival of only approximately 10% (117). The secondary cancer (SECA–1) study was an open prospective pilot study to assess the possible benefit of LT for patients with NCLM. From 2006 to 2012 twenty-three patients underwent LT. Since the first few experiences with LT for NCLM the field has developed. The rationale behind the study was:

1. **Improved surgical techniques**
2. **New immunosuppressing drugs**
3. **Improved preoperative imaging**
4. **Availability of liver grafts**

1.3.1.1 Improved surgical techniques

Increased experience and improved surgical techniques have improved OS after LT in general significantly over the last 20–30 years. According to the NLTR, 1– and 5–year survival was 61% and 53% in the period 1983–1994 (138). The corresponding data for the period 2004–2013 was 90% and 80% (139). These numbers include all LT indications including advanced liver cirrhosis, fulminant acute liver failure and malignant tumors. Since CRC patients do not commonly have portal hypertension and other cirrhosis associated complications, they are considered to be less complicated to operate than cirrhotic patients (138). Due to the increased experience of transplant surgeons and improved survival rates after LT in general the last 30 years, fever complications and improved outcome after LT for NCLM was expected compared to the reported experiences prior to 1995.

1.3.1.2 New immunosuppressing drugs

Organ transplantation requires lifelong immunosuppression and there is a balance between inhibition of allogenic immune mediated destruction of the organ and side effects. It is well documented that long term immunosuppression increases the incidence of long term *de novo* malignancy (140, 141). *De novo* cancers and cancer recurrence may be promoted by immunosuppression due to various mechanisms that include decreased immunosurveillance (142), facilitated action of oncogenic viruses (143) and direct alteration of DNA (144). These mechanisms differ between immunosuppressant drugs and cancer subtypes. Organ transplant recipients have an increased risk of malignant disease post–transplant of about 2–3 times compared to the general population (145, 146). Liver transplantation is associated with a 2 to 7–fold increase in the risk of *de novo* malignancy, with non-melanoma skin cancer, lymphoproliferative malignancy and solid tumors accounting for 37%, 25% and 48% of the malignancies (147). Traditionally, the immunosuppression following LT has been based on calcineurin inhibitors (CNIs) which might accelerate cancer growth (148).

In a systematic review and meta–analysis from 2010, Sint Nicolaas *et al.* reported a 2.56–fold increased risk of CRC after LT (149). Patients receiving LT for primary sclerosing cholangitis and inflammatory bowel disease have a 25% risk of developing

CRC post LT (150). Consequently, Herrero *et al.* have suggested intensified cancer surveillance after LT (151). It has also been suggested that *de novo* malignancy after transplantation behave more aggressively compared to malignancies in the general population (147). Patients diagnosed with CRC post transplantation are diagnosed at a younger age than the general population (59 years versus 72 years) (152, 153). Five–year OS from CRC diagnosis is reported to be significantly lower in transplant recipients compared to the general population (152, 153), especially for stage III disease (Duke C) patients with 5–year OS of 20% versus 65% (153). In a study from Australia and New Zealand, Verran *et al.* reported that patients developing CRC after LT had more advanced disease at diagnosis and poorer outcome with median OS from time of diagnosis of metastatic CRC of only two months (154). These results indicate a significant decreased OS after CRC diagnosis in transplant recipients compared to the general population.

The agent sirolimus has shown anti–angiogenetic effect and direct inhibitory effect on tumor growth combined with an immunosuppressive effect by blocking the intracellular pathway complex mammalian target of rapamycin (mTOR) (155). mTOR inhibitors have also shown clinical effect and radiological response in advanced breast and renal cancer (156, 157). A recent metaanalysis including 5924 renal transplanted patients with a mean follow–up of 41 months concluded that malignancy was significantly reduced during mTOR inhibitor treatment compared to CNIs (P=0.046) and that this effect was still retained when mTOR was combined with CNIs (P=0.05) (158). The SILVER study, which was a randomized trial between CNI and mTOR after liver transplantation for HCC, showed that patients receiving sirolimus following LT for HCC had a DFS and OS benefit the first 3–5 years, and this effect was particularly evident in the low risk patients (159).

The combined anti–cancer and immunosuppressive properties of mTOR inhibitors support the use of these drugs for patients with high risk of CRC metastases following LT like the SECA–1 cohort. In the SECA–1 study the conventional CNI treatment was replaced by mTOR inhibitors, and this option was not available for the patients who underwent LT for NCLM during the 1980s and 1990s. Due to the anti–proliferative properties of mTOR inhibitors some patients had wound healing difficulties and

developed ventral hernias. In these cases, the mTOR inhibitor was temporarily replaced by CNI (takrolimus/Prograf) in conjunction with surgical hernia repair.

1.3.1.3 Improved preoperative imaging

Only low–quality CT and US were available in the preoperative assessment of the patients who underwent LT for NCLM before 1995. Since then, preoperative imaging has developed and improved profoundly. These improvements are vital in the selection of NCLM patients that might have maximal benefit from LT.

- **Contrast enhanced CT (CECT)**: CT scanners with only a few detectors making thick slices (5 or 10 mm) with low resolution and without the possibility of MPR have been replaced by contrast enhanced spiral and multidetector CTs (CECT). The last generations CT scanners have the possibility of scanning large body volumes in only a few seconds, thinner slices with higher resolution and MPR. CECT is the workhorse in initial diagnosis and follow–up of CRC and most other malignant diseases. Also, CT can be used to guide tissue sampling of suspected metastatic lesions. Consequently, these properties of CECT are important in the selection of patient considered for LT.

- **MRI:** The last decade MRI has been implemented in the assessment of CRC patients. The most frequent indications are initial staging of rectal cancer, assessment of possible colorectal metastases in the liver, pelvis or bone and in assessment of possible local pelvic recurrence. High spatial resolution, diffusion sequences and the use of contrast agents makes MRI suitable to assess suspected liver metastases. Lesions < 10 mm are often difficult to determine by CECT but can be clarified by MRI.

- **Contrast enhanced ultrasound (CEUS):** Ultrasound is frequently used to guide tissue sampling (cytology/biopsy) and CEUS is often used in the assessment of liver lesion to rule out metastases.

- **PET/CT:** Prior to the year 2000 PET/CT was not routinely used in CRC. As previously discussed, ^{18}F–FDG PET/CT has been proven to be sensitive in detection of metastases not detected by CECT prior to possible metastasectomy. All SECA patients had NCLM and the possibility of

extrahepatic metastases was high making ^{18}F–FDG PET/CT a proper and important modality in this clinical setting.

These amendments in imaging tools have contributed substantially to improved patient selection. Based on the advantages of the separate imaging modalities, a combination of these are frequently used in the assessment of CRC patients, both in the initial staging and the subsequent evaluation.

1.3.1.4 Availability of liver grafts

Shortage of available donors in relation to the number of waiting recipients is the main limiting factor in most transplantation programs worldwide and NCLM is therefore generally not accepted as an indication for LT. Scandiatransplant is the common organ exchange organization for the Nordic countries. Due to low incidence of hepatitis C virus infections, hepatocellular carcinoma and alcoholic hepatitis compared with most countries, Norway has had short waiting time. In the early 2000s there was a deceased donor pool in Norway of about 25 per million inhabitants (PMI), but the LT rate was only about 20 PMI. This unique situation provided access to liver grafts, thus enabling an evaluation of the efficacy of LT for NCLM without negatively impacting other patients on the national liver transplant wait list.

1.3.2 Study logistics

Information about the SECA–1 study was sent to all university hospitals in Norway. Patients considered to have NCLM following chemotherapy were referred to Oslo University Hospital (OUH) for second opinion concerning resectability. Resectability was determined on the basis of the number and localization of the liver metastases. Up to 75% of the liver tissue can be removed, dependent on the location of the lesions and the quality of the remaining tissue. The liver remnant tissue regenerates to almost normal liver size within a few months. A prerequisite is that the remaining liver tissue has a portal vein, hepatic artery, hepatic vein and a draining bile duct preserved. If these structures are irreversibly impacted by the disease or the proposed surgical plan, the liver metastases are nonresectable. Patients considered nonresectable and having liver only disease at the multidisciplinary hepatobiliary meeting at OUH, were admitted to evaluation in the transplantation unit. After signing an informed consent, these patients underwent regular transplantation work–up

including CECT of thorax, abdomen and pelvis and a whole body ^{18}F–FDG PET/CT. If all inclusion criteria were fulfilled and no exclusion criteria were present, the final approval for inclusion to the study was performed at the multidisciplinary transplant team (MDT) meeting. Approved patients were put on the LT list and LT was performed according to the standard OUH procedures if no contraindications became apparent between the time of listing and the availability of a liver graft.

1.3.3 Inclusion criteria

1. Verified colon or rectal carcinoma (histology).
2. Liver metastases not available for curative liver resection.
3. No evidence of local recurrence assessed by CECT and MRI within 6 weeks prior to the MDT meeting.
4. No evidence of local recurrence assessed by colonoscopy less than 3 months prior to the MDT meeting.
5. No evidence of extrahepatic metastases assessed by CECT or MRI and FDG PET/CT of thorax, abdomen and pelvis within 6 weeks prior to the MDT meeting. Bone scintigraphy should be performed.
6. Age 18–60 years (upper age limit was subsequently raised to 65 years).
7. Good performance status, ECOG 0 or 1.
8. Minimum 6 weeks of chemotherapy.
9. Hemoglobin > 9 g/100ml, Neutrophil granulocytes > 1.0 x 10^9/L, Thrombocytes > 50 x 10^9/L and Creatinine < 1.25 x upper reference limit.
10. Undergone work–up and accepted for LT.
11. No evidence of pulmonary metastases assessed by chest CT at time of intended LT.
12. No evidence of malignancy on peroperative frozen sections from lymphatic nodes in the hepatoduodenal ligament and adjacent tissues.
13. Signed informed consent.

1.3.4 Exclusion criteria

1. Bevacizumab (Avastin®) treatment last 6 weeks.
2. Weight loss > 10% the last 6 months
3. Body mass index > 30
4. Known rapamycin hypersensitivity
5. Other general contraindications to LT
6. Other malignancy
7. Previous transplantation
8. Pregnant or breast–feeding women
9. Patients considered to not benefit from LT based on an evaluation by the project group or patients not able to follow the treatment according to the protocol.

1.3.5 Immunosuppression protocol

The patients in the SECA–1 study received immunosuppression according to the study protocol, which comprised induction of basiliximab and subsequent maintenance with a regimen containing sirolimus, mycofenolate mofetil and corticosteroids. In addition, all patients received aspirin to prevent arterial thrombosis. More details concerning the immunosuppression is given in the following table:

Day after LT	Simulect[1]	Glucocorticoids[2]	Rapamune[3]	Cellcept[4]
0	20 mg	540 mg i.v.		
1	0	80 mg	4 mg	0,5 g x 4
2	0	80 mg	4 mg	
3	0	70 mg	4 mg	
4	20 mg	60 mg	4 mg	
5		50 mg	4 mg	
6		40 mg		
7		30 mg	Dose based on serum consentration	
8–21		20 mg		
22–30		20 mg		
>31		→ 5 mg or 0 mg		

1 Basiliximab, an interleukin–2 receptor antibody

2 Solumedrol intravenously, Prednisolone per os

3 Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor
Day 6–28, 5–10 ng/ml, Day 29–365, 10–15 ng/ml
If side effects were observed: 5–10 ng/ml

4 Mycophenolate mofetil, an inosin mono– phosphate dehydrogenase inhibitor

1.3.6 Clinical outcome

Estimated 1, 3, and 5–year survival in the SECA–1 patients were 95%, 68% and 60% (*Figure 5*) (160). The 95% confidence interval at 5 years was 34% to 85%. Median (range) follow–up was 27 (8–60) months and DFS at 1 year 35%. Largest tumor diameter in the liver <5.5 cm, time from primary cancer surgery >2 years, CEA level <80 μg/L and response or stable disease on chemotherapy at time of LT were associated with improved OS (160). All patients developed recurrent disease. About 2/3 of the first site recurrences were pulmonary metastases, and many of these were accessible for surgical resection. Patients with pulmonary metastases without liver recurrence had significantly improved survival compared to the patients with hepatic metastases following LT (P = <0.001) (161).

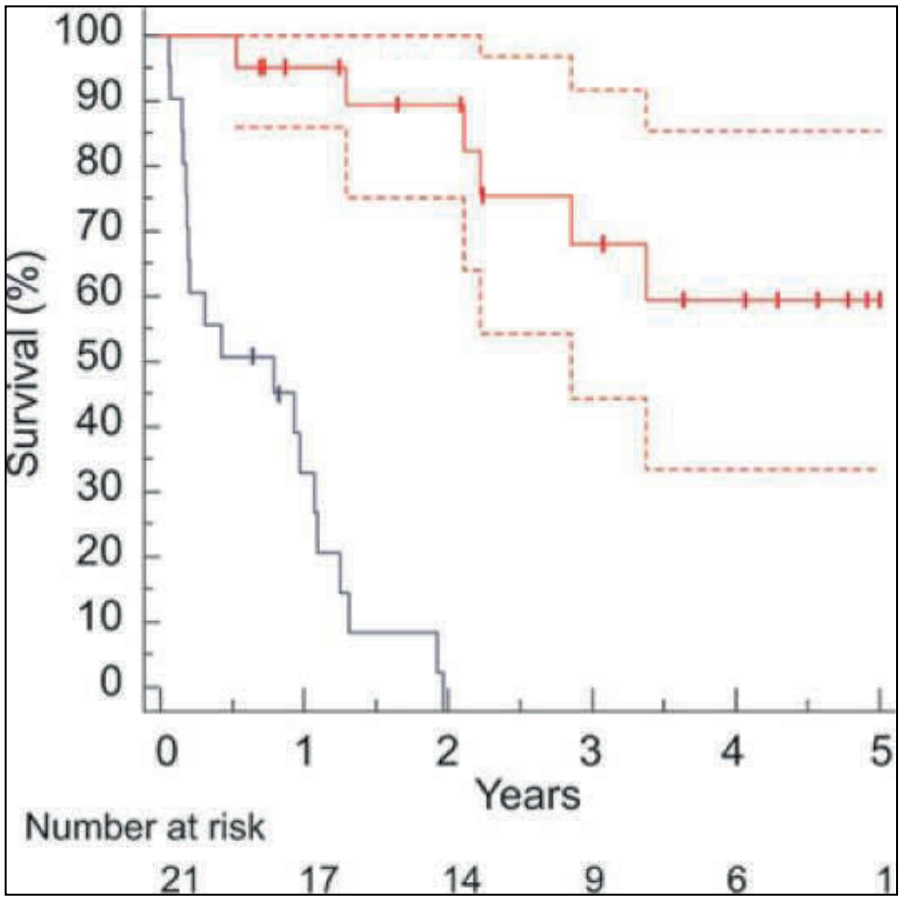

Figure 5: *Kaplan–Maier survival plot of the 21 first SECA–1 patients. Red line shows overall survival (OS) and blue line disease free survival. Estimated 5–year survival was 60%. The stapled lines show 95% confidence interval for OS. Re–printed with permission from senior author (160).*

2. AIMS

The overall aim of this thesis was to provide further knowledge of the diagnostic and prognostic utility of the imaging performed in the patient cohort that was considered for and who underwent LT for NCLM with a main focus on ^{18}F–FDG PET/CT.

Aims for each paper were as follows:

PAPER I

To assess if immunosuppressive therapy accelerates the growth of pulmonary metastases in patients transplanted for NCLM evaluated by CT.

PAPER II

To evaluate the prognostic value of volumetric and metabolic information assessed by ^{18}F–FDG PET/CT prior to LT in patients with NCLM.

PAPER III

To evaluate the performance of ^{18}F–FDG PET/CT for the selection of patients with NCLM to LT compared with CECT.

3. SUMMARY OF PAPERS

PAPER I

Growth Rates of Pulmonary Metastases after Liver Transplantation for Unresectable Colorectal Liver Metastases

Previous studies have shown that pretransplant malignancy are associated with an increased risk of all–cause and cancer–specific mortality, and of developing *de novo* malignancies after transplantation compared with rates in patients without pretransplant malignancy (162). Accelerated growth of metastases developed after LT for NCLM due to the immunosuppression was one of the concerns during the planning of the SECA–1 study.

In this paper chest CT scans from 11 SECA–1 patients resected for 18 pulmonary metastases were reviewed. Tumor diameter, volume and CT characteristics were registered and tumor volume doubling time (DT) was calculated. The SECA–1 patients were compared with a control group consisting of 12 advanced rectal cancer patients receiving standard treatment that were resected for 26 pulmonary metastases. DFS and OS after first pulmonary resection were determined.

Median DT based on tumor diameter and volume in the SECA–1 group and control group were 125 and 130 days (P = 0.66) and 110 and 129 days (P = 0.63). Median (range) DFS after LT in the SECA–1 group and primary surgery in the control group was 17 (6–42) and 18 (2–57) months (P = 0.53). Estimated 5–year DFS and OS in the SECA–1 group were 39% and 51% after first resection.

These results suggest that patients treated with LT for NCLM have a good prognosis following resection of pulmonary metastases and the immunosuppression used after LT did not have any significant impact on tumor DT.

PAPER II

The Prognostic Value of ^{18}F–FDG PET/CT Prior to Liver Transplantation for Nonresectable Colorectal Liver Metastases

All patients considered for LT for NCLM in the SECA–1 study underwent ^{18}F–FDG PET/CT to exclude extrahepatic disease. Patients with suspected extrahepatic disease were excluded from the study. This paper evaluated the prognostic value of metabolic and volumetric metrics measured from the ^{18}F–FDG PET/CT examination for the transplanted patients.

Maximum, mean and peak standardized uptake values (SUV_{max}, SUV_{mean} and SUV_{peak}), tumor to background (T/B) ratio, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were measured and calculated for all liver metastases. Total MTV and TLG were calculated for each patient. The patients were dichotomized by a cut–off value determined by a receiver operating characteristic (ROC) analysis for each of these parameters. One, three and five–year overall survival (OS) and disease free survival (DFS) for patients over and under the cut–off value were compared by using the Kaplan–Meier method and log rank test.

Twenty–three patients underwent LT in the SECA–1 study. Total MTV and TLG under the cut–off values were significantly related to improved OS at three and five years (P = 0.027 and 0.026) as well as DFS (P = 0.01). SUVs and T/B–ratio were not significantly correlated to OS and DFS.

Conclusively, total MTV and TLG from ^{18}F–FDG PET/CT prior to LT can potentially improve the patient selection for LT.

PAPER III

Importance of ^{18}F–FDG PET/CT to Select Patients with Nonresectable Colorectal Liver Metastases for Liver Transplantation

Many patients were excluded from the SECA–1 study due to detected extrahepatic disease on the preoperative imaging. The objective of this paper was to evaluate the utility of ^{18}F–FDG PET/CT for the selection of patients with NCLM for LT compared with CECT.

^{18}F–FDG PET/CT and CECT examinations prior to tentative LT for NCLM were assessed and findings contraindicating LT were registered. SUV_{max}, SUV_{mean} and SUV_{peak}, T/B–ratio, MTV and TLG were measured and calculated for all liver metastases. Results from patients with and without extrahepatic disease on ^{18}F–FDG PET/CT were compared by using the non–parametric Mann-Whitney *U* test. OS was calculated by the Kaplan–Meier method.

Thirty–two patients excluded by imaging were identified. ^{18}F–FDG PET/CT from 20 of the 32 excluded patients revealed extrahepatic disease. Eight of the other 12 patients had a negative ^{18}F–FDG PET/CT but were excluded by CECT. Ten patients were excluded by ^{18}F–FDG PET/CT only. Four patients were excluded due to detected malignancy from frozen sections at the start of the intended transplant operation. T/B–ratio of the liver metastases was significantly higher in patients where ^{18}F–FDG PET/CT detected extrahepatic disease ($P = 0.03$).

Conclusively, the ability of ^{18}F–FDG PET/CT to detect extrahepatic disease prior to LT for NCLM is vital to establish LT as a treatment option.

4. DISCUSSION

The study population in this thesis was patients who underwent LT and were considered for LT for NCLM in the SECA–1 study at Oslo University Hospital. In the period 2006–2012, a total of 23 patients underwent LT and 32 patients were rejected LT due to the detection of extrahepatic disease on the pre–LT CECT or ^{18}F–FDG PET/CT. It is important to keep in mind that the patients in the SECA–1 study are highly selected and that the number of patients is small. Thus, the findings have to be interpreted with caution. However, the study is the only of its kind worldwide, and the results and experience from this study has initiated further studies to improve the concept. There are several topics to be discussed in this thesis. In the following sections material and methods, statistical analyses and results from the three papers will be discussed. *Figure 6* shows an overview of the included papers.

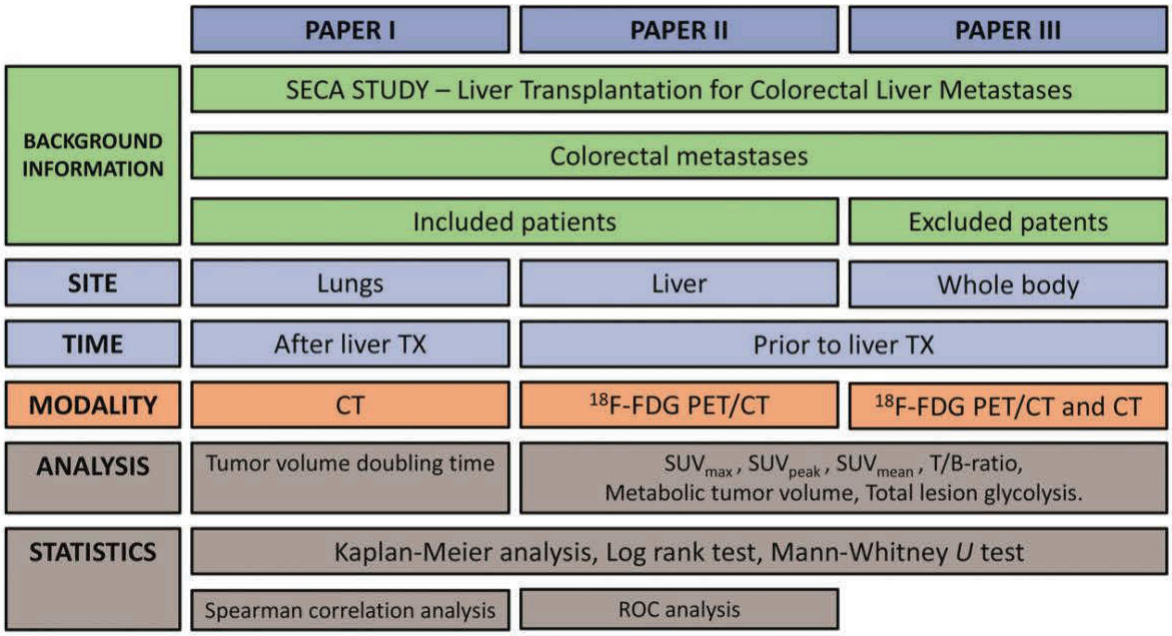

Figure 6: *The figure shows an overview the patients included, sites of metastases, imaging modalities, analysis and statistics for the three separate articles included in the thesis. TX = transplantation.*

4.1 Material and methods

Due to heavy tumor load in many patients and that all patients had nonresectable liver metastases the risk of recurrent disease following LT was considered to be high. Furthermore, accelerated growth of these metastases due to immunosuppression was one of the concerns in the planning of the SECA–1 study. All transplanted patients developed metastases and the lungs were the first metastatic site in 2/3 of the patients.

In **paper I** we wanted to evaluate the growth rates of these pulmonary metastases to assess whether the immunosuppression used after LT led to accelerated metastatic growth rates compared with pulmonary metastases in non–transplanted patients not receiving immunosuppression. The study group consisted of 11 SECA patients (10 SECA–1 and one SECA–2 patient) who had undergone resection of 18 pulmonary metastases following LT. The control group consisted of 12 rectal cancer patients primarily treated for locally advanced disease and subsequently resected for 26 pulmonary metastases. These patients were obtained from a prospective registered institutional rectal cancer registry.

According to the study protocol, the SECA–1 patients had undergone chest CT every 3 months the first year, every 6 months the second year and once a year 3–10 years after transplantation. The control group followed the national follow–up plan until 5 years after surgery. A limitation to the study is that the CT scans were performed on different scanners as a part of follow–up either at the transplantation unit or at local hospitals. This reflects the regular clinical routine work where the local hospitals are an important contributor in the follow–up of CRC patients. Optimally, all CTs should have been performed at the same scanner with the same protocol.
However, all CT scans were imported to a Siemens syngovia work station and retrospectively reassessed by two dedicated radiologists to achieve consensus.

Largest diameter and volume of the metastases during follow–up were obtained by using a built–in semiautomated function delineating the metastases from the normal lung tissue. All measurements were manually controlled and adjusted if needed. In some cases, it was difficult to delineate the metastases from adjacent tissue like arteries/veins because the attenuation was similar to the metastases. In these cases,

the delineation was done manually by the two radiologists. Also, the tumor volume at the last CT prior to the pulmonary resection was significantly correlated to the diameter measured at histological examination following resection (correlation coefficient 0.78, $P < 0.001$), making the radiological measurements reliable. *Figure 7* shows an example of diameter and volume measurements done in one pulmonary metastasis. Tumor volume doubling time (DT) based on both the obtained diameters and volumes was calculated by using a modified version of the Schwartz equation (163):

$$\text{DT (diameter)} = (T_{\text{last CT}} - T_{\text{first CT}}) \cdot \frac{\log 2}{3 \cdot \log \frac{D_{\text{first CT}}}{D_{\text{last CT}}}}$$

$$\text{DT (volume)} = (T_{\text{last CT}} - T_{\text{first CT}}) \cdot \frac{\log 2}{\log V_{\text{last CT}} - \log V_{\text{first CT}}}$$

$T_{\text{last CT}} - T_{\text{first CT}}$ is the time between the CT scan where the metastasis was detected and the last CT scan before resection, $V_{\text{last CT}}$ and $V_{\text{first CT}}$ are the tumor volumes and $D_{\text{last CT}}$ and $D_{\text{first CT}}$ are the tumor diameter at these two time points.

The Schwartz equation was used under the assumption of exponential growth and widely used to assess tumor growth during follow–up (164, 165). Low DT reflects rapid tumor growth and high DT reflects slow tumor growth. Largest diameter on axial CT sections (Response evaluation criteria in solid tumors, RECIST) is more often used in clinical routine than tumor volume (166). However, from a tumor biological viewpoint, tumor volume is probably more correct due to the commonly observed irregular shape of different tumors. Thus, we calculated DT based on both diameter and volume. Gompertzian growth could have been an alternative model. This model has a sigmoid growth curve with an early almost exponential shape and, in contrast to the Schwartz model, it is followed by a slower growth rate which reaches a plateau as the tumor grow larger in size (167, 168). In our study we only evaluated small pulmonary metastases and the Schwartz model was considered to be the most adequate.

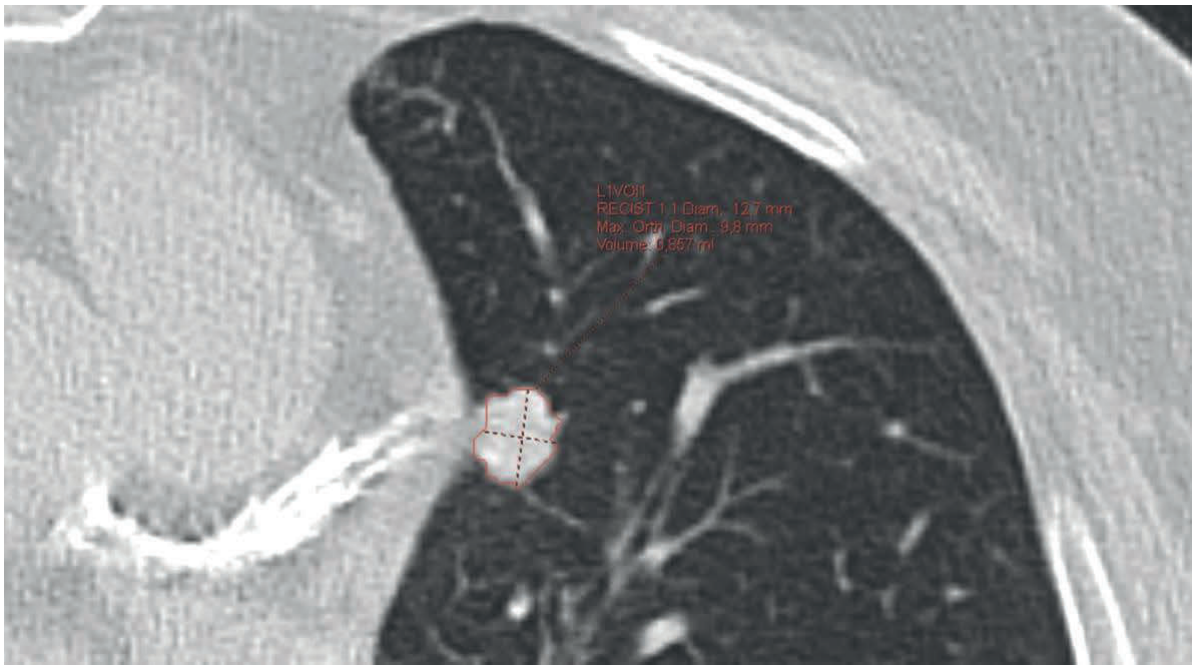

Figure 7: *Example of diameter and volume measurements obtained by using Siemens syngovia software in a patient with a pulmonary metastasis in the left upper lobe.*

The control group developed only pulmonary metastases after primary rectal surgery whereas to the SECA–1 group developed pulmonary metastases following LT for NCLM. Consequently, both groups consisted of highly selected patients with possible differences in tumor biology. Following primary surgery in the control group and following LT in the SECA group, all patients developed resectable lung only metastases. The control group include pulmonary metastases from rectal cancer only, compared with the SECA group consisting of 6 patients with colon and 5 patients with rectal cancer. There was no difference in OS from the first pulmonary resection between patients having a colon and rectal primary cancer (P = 0.65) in the SECA group. An alternative control group could have been patients resected for pulmonary metastases following resection for colorectal liver metastases, but such a comparator group can be difficult to identify.

Proliferation markers (e.g. Ki67) and genomics to make a more profound comparison of the two groups should preferably been done. Unfortunately, these analyzes have not been performed. Histopathology examination of resected lesions confirmed pulmonary metastases with colorectal origin in all included patients. In the SECA group the pulmonary metastases were moderately differentiated in 11–12 % and not

specified in 88–89% of the patients. The primary tumor was moderately differentiated in about 70% and not specified in about 30% of the patients. In the explanted liver 64% were moderately differentiated and not specified in 36%.

Paper II and **paper III** were PET focused studies and evaluated the prognostic value of PET derived uptake measurements from the liver metastases from the included (n=23) and excluded (n=32) patients and the ability of ^{18}F–FDG PET/CT to detect excluding extrahepatic disease compared to CECT in the excluded patients. From the ^{18}F–FDG PET/CT prior to tentative LT, SUV_{max}, SUV_{mean}, SUV_{peak}, MTV and TLG and tumor to background ratio (T/B-ratio) from the liver metastases were measured and calculated by using Siemens syngovia software (version VB10A, Erlangen, Germany) as previously described.

A fixed threshold of 40% was chosen to delineate the liver metastases. The choice of threshold was discussed and decided prior to our study. There is no consensus about what threshold to use when delineating tumors in PET. Some studies use absolute SUVs (e.g. 2,5) and others use threshold as a percentage of the SUV_{max} (fixed or adaptive threshold). For fixed threshold, values of 15–60% have been used, and most commonly 40% has been chosen. A 40% fixed threshold is also the default value in the software (Siemens, syngovia) used in this study and in the routine work. Therefore, this value was chosen. When performing the measurements, we also observed that this value delineated the liver metastases adequately. The European Association of Nuclear Medicine (EANM) has suggested a threshold of 41% in lesions with high tumor to background ratios and 50% in lesions with low tumor to background ratios (169).

Unfortunately, the PET protocol used was not uniform for all patients. EAMN gudelines for FDG PET tumor imaging recommend a time interval of 60 minutes from FDG injection to PET scan with an acceptable range of 55–75 minutes (169). Out of the total 55 PET scans performed and included in this thesis, seven (13%) had time interval from injection to scan of more than 75 minutes. Preferably all scans should have been within the recommended time interval to get as comparable measurements and reliable assessments of the PET findings as possible.

To optimize the FDG uptake in tumor cells and ensure that it is not wasted on physiological uptake the glucose levels should preferably be within normal limits. The EAMN guidelines states that efforts should be made to have normal glucose levels (4–7 mmol/L) prior to FDG PET scan (169). However, for clinical and research studies the guidelines recommend normal glucose levels up to 11 mmol/L and 8.3 mmol/L, respectively. Patients with glucose levels above this should be rescheduled or the patient should be excluded depending on the circumstances. One of the 23 included SECA patients had a glucose level of 12.1 mmol/L and three of the 32 excluded SECA patients had glucose levels of 8.9, 8.9 and 11.7 mmol/L. These high glucose levels were not optimal with respect to the PET scan. However, in some clinical settings it is more important to get a fast, sub–optimal examination as scheduled than an optimal delayed examination. For the patients considered for inclusion to the SECA study, a rescheduled PET could imply delayed chemotherapy and delayed evaluation at the MDT meeting, with possible negative impact on the prognosis.

Some patients received a dose of ^{18}F–FDG that was not strictly correlated to weight. For example, approximately 370 mega becquerel (MBq) ^{18}F–FDG was given to patients with normal weight, and slightly higher dose was given to patients with overweight. Standard dose, directly correlated to weight for all patients is recommended (e.g. 2.5 MBq/kg).

The ^{18}F–FDG PET/CTs in the SECA study followed a standard protocol and was not optimized for detection of liver metastases or extrahepatic metastases in the upper abdomen. Physiologic ^{18}F–FDG uptake in the liver and respiratory movements cause a smearing of focal ^{18}F–FDG uptakes. Possible erroneous attenuation correction due to phase mismatch between the PET and CT could have further influenced the performance of the examination (44, 170). To cope with respiratory movements and to improve the sensitivity of ^{18}F–FDG in general, new techniques have been introduced since the SECA–1 study (171, 172). This will be further discussed in the subsequent *future perspectives* of the thesis.

Chemotherapy can cause a *metabolic shutdown* in the tumor tissue causing decreased FDG uptake for several weeks, and in some cases up to 3 months after administration. The included SECA–1 patients and the excluded patients had a

chemotherapy–free interval exceeding 4-6 weeks prior to the ^{18}F–FDG PET/CT (45, 173). Consequently, the FDG uptake could have been underestimated leading to fewer liver metastases detected by the PET and lower SUVs and metabolic tumor volumes.

A limitation with **paper II** is the long time interval between ^{18}F–FDG PET/CT and LT in some patients with a median time of 70 days (range 12–273 days). This could have led to a progression of the disease in the patients with a long interval. An additional statistical test that compared the patients with interval time over and under the median value (70 days) showed no difference in MTV (P = 0.21) or TLG (P = 0.17) values between the two groups (Mann-Whitney *U* test). Furthermore, there was no difference in 3–year (P = 0.44) and 5–year (P = 0.11) survival (log rank test). Also, all patients were followed by an oncologist with clinical examinations, blood samples and CECT as a part of the regular follow–up for patients with colorectal liver metastases after the ^{18}F–FDG PET/CT until intended LT. Patients on the transplant list who developed extrahepatic metastases were not transplanted. At time of LT, an additional CT thorax was performed to exclude patients who had developed pulmonary metastases during the waiting period for LT. Consequently, it was considered appropriate to include all the SECA patients in this PET focused study.

In **paper II**, the patients were dichotomized for each of the PET parameters by finding cut–off values giving the best possible combination of sensitivity and specificity to predict survival by using a ROC analysis. OS and DFS for the patients with high and low values were compared for each of the PET derived parameters by a log rank test and Kaplan–Meier plot. It could be argued that the cut-off values from a ROC curve analysis would make the utmost differences between the two groups without necessarily having a general meaning. ROC curves are well known and regularly used to determine cut–off values, and several other FDG PET/CT studies on MTV, TLG and SUVs have also used ROC curves to dichotomize patient groups. Alternatively, the patients could have been divided into one group with values under and one group with values over the median for each of the PET parameters.

In **paper III,** excluding findings from CECT and ^{18}F–FDG PET/CT that were available on the MDT meeting (screening date) were registered. Median (range) time between

these two examinations was 19 (0–84) days. This time interval could have affected the stage of disease when the patents were assessed by CECT and ^{18}F–FDG PET/CT. However, median time interval was only 19 days and less than 3 months for all patients and thus considered to be acceptable. If CECT both prior and after the ^{18}F–FDG PET/CT were available, the findings in the report from the examination performed closest to the ^{18}F–FDG PET/CT was registered.

The registered causes leading to exclusion from LT were based on the *real time* findings in the routine reports. This reflects the actual imaging decision basis at the MDT meeting in routine work. An alternative method could have been a blinded assessment of the CECT and ^{18}F–FDG PET/CT by separate radiologists and nuclear medicine physicians. In our setting with patients evaluated for possible inclusion to the SECA study, the actual reports which were the basis of the evaluation at the MDT meeting were more clinically relevant than a constructed blinded research setting. Also, in most patients the previous CECT was available for comparison at time of the ^{18}F–FDG PET/CT, which could have interfered with the assessment. Both the imaging (CECT and ^{18}F–FDG PET/CT) and the imaging assessment of patients considered for the SECA study should optimally be done by dedicated physicians at the transplantation center at the same time point.

In addition to the 32 patients assessed in this paper, seven patients were excluded by non–imaging reasons. Three patients had body mass index >30, one patient had reduced performance status (ECOG >1), one patient suffered from depression, one patient developed ascites while waiting for a LT, and this was interpreted as extrahepatic involvement and one patient developed pulmonary metastases and was taken off the LT waiting list. All these patients had negative CECT and ^{18}F–FDG PET/CT initially.

A limitation to this paper is that the suspected extrahepatic disease detected by CECT and/or ^{18}F–FDG PET/CT was not necessarily confirmed by tissue samples (cytology/histology). However, in this clinical setting of patients considered to have NCLM, the *pretest probability* of confirming findings suspected to be extrahepatic metastases by these modalities was considered to be high. If these findings turned out not to be metastases during further follow–up, they could have been re-evaluated.

4.2 Statistical analysis

All statistical analyses were performed using SPSS version 24 (IBM, Armonk, New York, USA). P-value <0.05 was considered statistically significant for all papers.

OS was defined as time from transplantation to any cause of death. DFS was defined as time from transplantation to relapse of CRC disease like for example CT detected pulmonary metastases or other malignancy. OS and DFS data were estimated and visualized by the Kaplan–Meier method. Log rank test was used to determine whether differences in survival were significant between groups. A limitation to the Kaplan–Meier method is that is does not adjust for differences in the distribution of variables that could be associated with the likelihood of the outcome. Such variables are called confounders. An example of such a variable is age, which is associated to increased mortality.

Other groups of data were compared using the non–parametric Mann-Whitney *U* test. A non–parametric test was chosen due to the relatively small number of patients/observations in the papers and that the distribution of the separate parameters did not display a parametric distribution when evaluated by histograms.

In **paper I**, some patients had more than one metastasis included and these metastases were not completely independent. However, in patients with multiple metastases the growth rates were different for the separate lesions. This could be explained by a heterogeneity in tumor biology of the metastases in the same patient supporting the use of an independent statistical test. Furthermore, additional analysis comparing only the first pulmonary metastasis in the SECA–1 patients to only the first metastasis in the control group did not show any different DT. In **paper I**, DTs in the SECA–1 and control group were visualized by a box plot.

In **paper II** and **paper III** several statistical tests (SUVs, MTV, TLG, T/B-ratio) were performed on the same data set, and it could be argued that a correction to the P–value ($\propto$) like the Bonferroni correction should have been made. To perform a Bonferroni correction, the P-value ($\propto$) is divided by the number of comparisons (n) performed; $\propto$/n. The test is used to reduce the probability of obtaining a false positive

result (type 1 error) due to the fact that the probability of identifying at least one significant result increases as more hypotheses are tested. However, the correction is also equally associated with an increased probability of making a type 2 error, which means concluding there is no significant effect when there actually is one. Due to the low number of cases, this would leave the study strongly underpowered. Therefore, we simply chose to test against a P–value of 0.05. In these PET papers univariate analysis was used. It could be argued that a multivariate analysis should have been performed to assess the relation between the different variables. The sample size in these papers is small. To perform a multivariate analysis a large sample of data is needed, otherwise the results become meaningless due to high standard errors. The standard errors determine the level of confidence of the results and can be reduced by increments in sample size. Thus, univariate analysis was considered the best statistical approach in our PET studies.

4.3 Ethics

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all SECA patients. The SECA–1 study was an open prospective study with institutional and regional ethical board approval (S-05409 Regional Ethics Committee) and registered at ClinicalTrials.gov: NCT01311453.

4.4 Discussion of results

To our knowledge, no other research groups have ever neither assessed growth rates of pulmonary metastases following LT for NCLM nor the role of ^{18}F–FDG PET/CT in these patients. Thus, no directly comparable studies are available.

Paper I – Growth rates of pulmonary metastases

The results from **paper I** support pulmonary resection of metastases following LT for NCLM. The growth rates of the pulmonary metastases were not accelerated despite the immunosuppression used in the study. All SECA patients performed a chest CT at time of intended LT to rule out acquired pulmonary metastases while waiting for the transplant. A previous study has shown that 7 out of the 21 first SECA patients had pulmonary metastases at time of LT that were retrospectively detected at chest CT, but without having an impact on survival (161). These results emphasize the limitation of chest CT in the detection of very small lesions/nodules.

Despite different factors that could possibly influence the calculated growth rates of the pulmonary metastases, 5–year survival following first pulmonary resection was 51%, which is comparable to non-transplanted patients (128). This is important clinical information when decisions concerning treatment options of pulmonary metastases on the SECA patients are made. If the growth rates were increased and survival after pulmonary resection was low, these patients would probably be offered chemotherapy rather than surgical treatment.

Neither group received chemotherapy during CT follow–up of the pulmonary metastases. The SECA–1 group received chemotherapy prior to LT and the control group received capecitapine (825 mg/m^2 twice daily) during 5 weeks of radiotherapy prior to primary rectal surgery. If micro pulmonary metastases that were not detected by chest CT were present during this treatment, the growth of these metastases could have been inhibited by this treatment. The SECA–1 group received immunosuppression including mTOR inhibitor and aspirin following LT. Both these drugs have anti–tumor properties which could have inhibited the growth of the resected pulmonary metastases (174, 175). A recent Norwegian study that included 23162 patients showed that aspirin use after the diagnosis of CRC was independently

associated with improved CRC–specific survival and OS (174). The aspirin use of the control group was not determined.

The median tumor diameter/volume at detection was significantly lower in the SECA group compared with the control group. This could be related to the close follow–up of the SECA patients. The control group was followed at different hospitals and it could be that the follow–up was not that strict in this group, even though there is a national recommended guideline. Median (range) time from LT/primary surgery to pulmonary metastases ≥10mm was 17 (6–42) and 18 (2–57) months (P = 0.53, log rank test). Also, size at the last CT prior to pulmonary resection (P = 0.62 (diameter) and 0.69 (volume) and histological examination (P = 0.50) were the same. This further supports the hypothesis that larger diameter/volume at detection in the control group is due to less strict follow–up and not due to more aggressive tumor biology.

Median DT based on tumor diameter and volume in the SECA–1 group and control group were 125 and 130 days (P = 0.66) and 110 and 129 days (P = 0.63) (*Figure 8*). However, the DT ranges were wide for both groups. Range DT based on tumor diameter and volume in the SECA–1 group and control group were 27–430 and 35–282 days and 30–320 and 40–274 days, respectively. A previous study on the growth rates of CRC pulmonary metastases in non–LT patients showed similar DTs (165). This reflects the heterogenous nature of pulmonary metastases from CRC and probably CRC in general. Also, this point as a potential for patient selection by including only patients with indolent tumor biology.

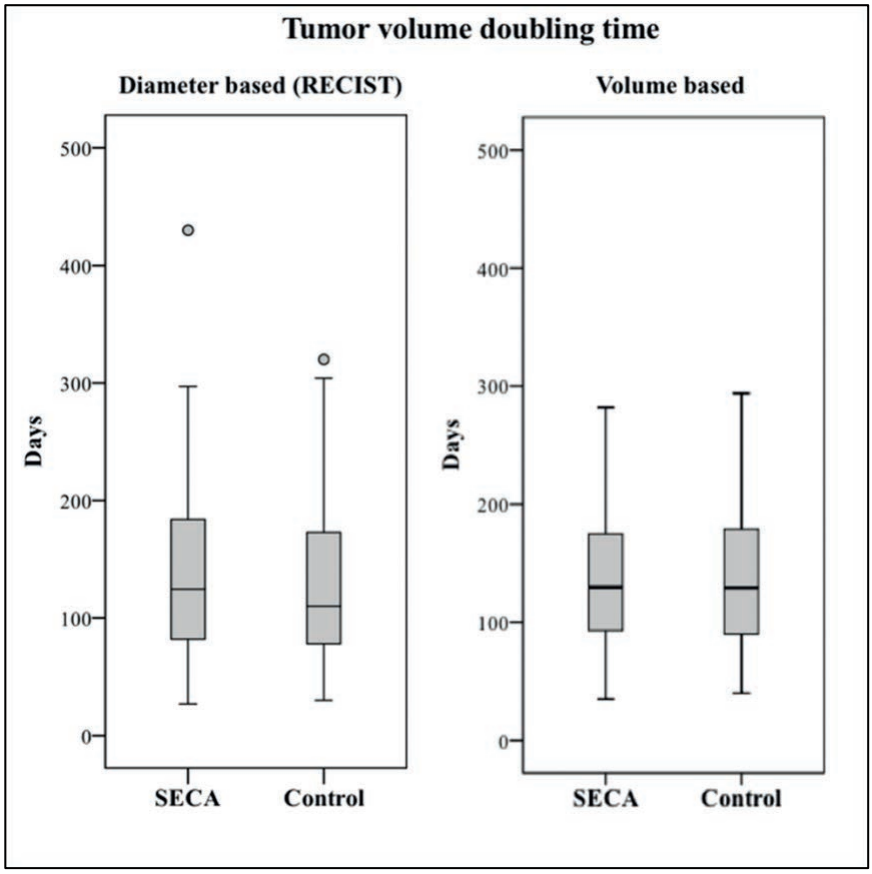

***Figure 8**: Box-plot. Tumor volume doubling time in the SECA group compared to the control group, both calculated by tumor diameter and tumor volume. There was no difference between the two groups (P = 0.66 and P = 0.63).*

Paper II / III: ^{18}F-FDG PET/CT as prognostic tool and in patient selection

In **paper II** we found that the liver transplanted patients with low values of MTV and TLG derived from the preoperative ^{18}F–FDG PET/CT had significantly increased 3 and 5–year OS and DFS in patients who underwent LT for NCLM. In **paper III** the T/B–ratio in the patients with detected extrahepatic disease on ^{18}F–FDG PET/CT was significantly higher than in patients without extrahepatic disease on ^{18}F–FDG PET/CT (P = 0.03). MTV and TLG reflect tumor burden and aggressiveness. It is likely that the possibility of extrahepatic disease not detected by the preoperative imaging in patients with high PET values is increased and consequently leads to impaired OS and DFS. Several studies have evaluated ^{18}F–FDG PET/CT as a predictor of overall prognosis and recurrence following LT for HCC (176-180). Most of these studies used conventional PET derived values (SUV_{max}, SUV_{mean} and T/B–ratio). Kim *et al.* showed that T/B–ratio and TLG was correlated to improved recurrence free survival after LT for HCC (176). As previously mentioned, no other studies have ever evaluated the prognostic value of ^{18}F–FDG PET/CT prior to LT for CRC. However, some studies have evaluated ^{18}F–FDG PET/CT in non–transplanted patients. In patients undergoing selective internal radiation therapy (SIRT) for CRC liver metastases with yttrium–90, volumetric and metabolic information from the pretreatment ^{18}F–FDG PET/CT have shown to predict progression free survival and prognosis (181-184). Also, post–SIRT ^{18}F–FDG PET/CT response evaluation predicted survival (181, 182, 184).

In addition to OS, MTV and TLG also predicted DFS in the SECA–1 patients. In contrast to HCC patients who most frequently relapse in the liver, 2/3 of the SECA–1 patients had the lungs as the first site of recurrence without this impairing OS (161). As shown in **paper I**, many of these metastases were accessible for surgical resection, the growth was not accelerated and the 5–year survival following first pulmonary resection was good (51%). This survival is comparable with 5–year survival in non–transplanted patients undergoing resection for pulmonary CRC metastases (38%–64%, median 53%) (161). Seven of the first 21 SECA–1 patients had a hepatic relapse. Six out of these seven patients were dead at the end of follow–up with a median time from detection to death of 14 months (range 4–21 months) (161). Thus, the ability of ^{18}F–FDG PET/CT to predict OS is more clinically important

than the ability to predict DFS. The ability to predict extrapulmonary first metastases was not evaluated.

Cut-off values were calculated for all PET parameters (SUVs, MTV, TLG and T/B-ratio) in **paper II**. It is important to emphasize that the particular cut–off values determined by this study cannot be generalized to other cohorts due to the highly selected and small patient cohort. I addition, the number of patients is currently too small for implementing these cut–off values into clinical practice in new SECA patients. Six out of 23 SECA–1 patients and 5 out of 15 SECA–2 patients had no visible liver metastases on the preoperative ^{18}F–FDG PET/CT. If these patients from both studies are pooled together and show improved survival, no visible liver metastases (negative PET) can potentially be an inclusion criterion. Negative PET is easier to implement in clinical practice than cut–off values. Oppositely, very high values of MTV and TLG could be an exclusion criterion like the different prognostic categories found in the first SECA–1 paper (largest tumor diameter determined by CT >5.5 cm, CEA > 80 μg/L, time from primary surgery to LT > 2 years and progression of disease during chemotherapy prior to LT) (160).

In **paper II**, twenty-three patients were evaluated. In general, this is a relatively low number and the results must be interpreted and used carefully and consequently, the conclusion in this paper is toned down stating that "Total MTV and TLG from ^{18}F–FDG PET/CT (…) can *potentially* improve the patient selection for LT". Preferably the number of patients should have been higher to strengthen the statistical analysis and clinical impact. However, despite that the number of patients was 23, the results showed significant differences. One should keep in mind that this is not the final word regarding the use of PET for LT patient selection, but rather one of the first steps. Also, worldwide, no one has ever performed a study like the SECA study by offering LT to patients with NCLM, and this study could be the first to possibly establish this as a potential treatment option and using ^{18}F–FDG PET/CT as one of the selection tools.

Results from **paper III** show that ^{18}F–FDG PET/CT detected extrahepatic disease that was not detected by CECT, which led to exclusion of many patients (31%) This included local recurrence and metastases to LNs in the upper abdomen, skeleton,

lungs and spleen. Median OS after exclusion from the SECA–1 study was 16 months. If these excluded patients had undergone LT, the 5–year OS in the SECA–1 study would probably be too poor to justify the use of liver grafts in NCLM, and the concept would have been abandoned, similar to the reports prior to 1995 (134-137). If the patients with extrahepatic disease were transplanted, the survival would probably be more than 16 months, but it is not likely that any of these patients would live five years after LT. In line with our results, a metaanalysis from 2015 including 1059 patients found extrahepatic disease in 32% of patients with suspected liver metastases, with a change of treatment management in 24%, most frequently from curative surgery to palliative chemotherapy (68). In several patients, a diagnostic (full dose) CECT detected extrahepatic disease not detected by ^{18}F–FDG PET/CT, for example small pulmonary metastases in several patients. Even though ^{18}F–FDG PET/CT includes the thorax, this is a low dose non–CECT with limited diagnostic value. This underlines the complementary properties of ^{18}F–FDG PET and diagnostic CECT. Several studies have shown that CRC can benefit from a combined ^{18}F–FDG PET/CECT instead of ^{18}F–FDG PET/ CT and a separate CECT. In the preoperative evaluation in the SECA–1 study the ^{18}F–FDG PET/CT and CECT were performed at two separate time points.

Four patients were excluded owing to proven malignancy on the routine histological examination of LNs of the hepatoduodenal ligament and/or adjacent tissue harvested during the initial staging at the time of laparotomy, despite both negative preoperative ^{18}F–FDG PET/CT and CECT. This could be explained by the limited spatial resolution in PET in general, and that the ^{18}F–FDG PET/CT protocol in the SECA–1 study was not optimized to correct for respiration motion in the upper abdomen. Despite optimization of the PET protocol, micro metastases will probably not be detectable and cannot replace a peroperative histological frozen section examination. Novel techniques to improve the sensitivity of PET and to cope with respiration movements will be further discussed in the *future perspectives* section. Finally, the long time interval from ^{18}F–FDG PET/CT to intended LT in some patients could have led to a progression of disease. This time interval was 52, 85, 110, and 249 days in the four patients excluded by frozen sections. Preferably, the latest imaging preceding LT should not exceed 3 months.

5. CONCLUSIONS

PAPER I

Patients treated by LT for NCLM have a good prognosis after resection of pulmonary metastases. DT did not appear to be worse with the immunosuppression used after LT.

PAPER II

Total MTV and TLG measured from ^{18}F–FDG PET/CT prior to LT for NCLM were significantly correlated to improved three and five–year OS and DFS and can potentially improve the patient selection for LT.

PAPER III

The ability of ^{18}F–FDG PET/CT to detect extrahepatic disease prior to LT for NCLM is vital to establish LT as a treatment option.

6. FUTURE PERSPECTIVES

6.1 Clinical perspectives

The SECA–1 study consists of highly selected patients. Only 23 patients were included between 2006 and 2012, and the vast majority of patients with NCLM are treated with palliative chemotherapy with poor prognosis. However, OS in patients treated by LT for NCLM exceeded by far previous reports for this patient group and the survival in patients treated by chemotherapy (117, 160, 185). Quality of life was good and symptoms after LT were minor (186). Also, an economic analysis indicated that LT for low risk NCLM is cost effective (187, 188).

Paper I shows that patients with pulmonary metastases following LT can be successfully resected and that the growth of the pulmonary metastases were not accelerated despite the immunosuppression used in the study (189). Based on the results from **Paper I**, a strategy where detection of small pulmonary nodules at chest CT at time of intended LT not should disqualify potential SECA patients may be considered.

The main challenge of transplantation programs worldwide is the scarcity of available donor grafts as opposed to the large number of waiting patients in need for transplant. Many of the patients who are put on the transplant list will die within short time if transplantation is not performed. Strict and clear priority criteria are necessary to prioritize individual patients on the waiting list. According to the Nordic Liver Transplant Registry the 5 most frequent diagnoses of patients undergoing LT in the period 2004–2013 were (139):

1. Primary sclerosing cholangitis 15.9%
2. Hepatocellular carcinoma (HCC) 12.0%
3. Alcoholic cirrhosis 11.2%
4. Post hepatitis C cirrhosis 10.4%
5. Acute hepatic failure 9.4%

Also, there are strict criteria for which donor livers that can be used. To alleviate the shortage of organs, *extended criteria donor* (ECD) grafts have been suggested, and

it has been argued that these grafts, which traditionally have been thought of as suboptimal or even marginal in the setting of portal hypertension and liver insufficiency, can be used safely through careful selection of both donor and recipients. There is no consensus on ECD, however some characteristics are frequently cited (190) :

- Advanced age
- Steatosis
- Donation after cardiac death
- Organ dysfunction at procurement
- Cause of death: anoxia or cerebrovascular accident
- Disease transmission:
    - Hepatitis B core antigen or antibody positive
    - Hepatitis C virus
    - Increased risk of hepatitis C and HIV
    - HIV positive
    - Extrahepatic malignancy
- Cold ischemia time > 12 hours

To justify the use of livers from the regular organ pool for patients with NCLM, OS should be comparable to other conventional transplant diagnoses. A recent publication showed that low risk SECA–1 patients had a 5–year OS of 75% compared with 76% in patients undergoing LT for HCC (191). According to the NLTR, the 5–year survival for HCC, secondary liver tumors and cholangiocellular carcinoma was 66%, 60% and 42% in the period 2004–2013 (139).

Due to the high OS in the SECA–1 cohort further studies were planned and are now ongoing (2018). Patients from the SECA–1 study with stable disease or response to chemotherapy at LT had significantly improved survival compared to patients with progression of disease (160). This fact is utilized in the SECA–2 study which evaluates if stricter inclusion criteria will achieve improved OS compared to the SECA–1 study and whether ECD grafts safely can be used for LT for NCLM and improve OS.

SECA–2

The main goal of the SECA-2 study is to achieve a 5–year OS of 75%. The study consists of 4 arms and is currently (2018) including patients.

Arm A: Patients with resectable liver metastases were randomized to either resection or LT. This arm was stopped after inclusion of 2 patients due to lack of patents.

Arm B: Patients with metachronous NCLM and minimum 10% response to chemotherapy according to the RECIST criteria and more than one year since primary diagnosis were offered LT with liver from the regular donor pool.

Arm C: Patients with synchronous NCLM and minimum 10% response to chemotherapy according to the RECIST criteria and more than one year since primary diagnosis were offered LT with liver from the regular donor pool.

Arm D: Patients with NCLM and expected survival of 6–12 months are offered LT with ECD. In this arm patients without minimum 10% response to chemotherapy, less than 1 year since primary diagnosis and resectable pulmonary metastases are accepted.

SECA–3

Patients with NCLM and expected survival of 6–12 months without signs of extrahepatic disease on ^{18}F–FDG PET/CT, CECT of thorax/abdomen/pelvis and pelvic MRI and progression or intolerance to 1st line chemotherapy are randomized 1:1 to either LT with ECD or 2nd line chemotherapy. Patients with resectable pulmonary metastases are also accepted.

The RAPID concept

This study is designed to accommodate the lack of liver donors by utilizing one donor liver for two patients. The patients have NCLM and expected survival of 6–12 months without LT and patients with 1 to 3 pulmonary metastases <15 mm are also accepted. The LT is performed according to the *RAPID concept* (**R**esection **A**nd **P**artial Liver Segment 2/3 Transplantation With **D**elayed Total Hepatectomy), a 2-step procedure

(192). First a partial hepatectomy of the left liver avoiding cutting thorough metastatic tissue directly followed by an orthotropic LT of liver segment 2 to 3 from a deceased donor. The right liver portal vein is ligated to stimulate and accelerate liver regeneration. During graft regeneration, only immunosuppression is given. Repeated CT scans with volumetry of the transplanted liver segments is performed weekly to evaluate the graft regeneration. When the donor graft (liver segment 2 to 3) reached a size of 0.8% of body weight or 35% to 40% of recipient standard liver volume a completing second hepatectomy of the right remnant liver is performed leaving patient with donor segments alone and thereby free from liver metastases.

Strict patient selection criteria are vital to select the patients who will benefit from LT. However, more studies are needed if NCLM is going to be established as an accepted indication for LT and to allow usage of livers from the regular donor pool. Worldwide, the lack of organ donors is the main limitation for adding NCLM to the list of accepted LT diagnosis. Extended donor criteria and the RAPID concept can possibly contribute in this context. The SECA–2 and SECA–3 studies can provide further knowledge on these issues. Also, if the RAPID concept is successful and can be extended to living donors, this could have huge implications on the number of patents that can be offered LT. All studies on LT for NCLM should be performed in controlled prospective studies, and an international registry collecting and analyzing data would have high scientific value. Furthermore, harmonized protocols for all studies would represent substantial clinical value.

6.2 Imaging perspectives (PET)

The results from this thesis show the important role of ^{18}F–FDG PET/CT in the patient selection (**Paper III**) and point out this examination as a potential prognostic tool (**Paper II**) in patients undergoing or considered for LT for NCLM. However, since the SECA–1 study (2006–2012), the PET technology has improved.

6.2.1 Improved PET technology

There are two main limitations of PET imaging: (1) low spatial resolution leading to partial–volume effect and (2) low signal–to–noice ratio (SNR). The ^{18}F–FDG PET/CTs in the SECA–1 study were performed on analogue PET scanners installed in 2004. Since then, new acquisition methods, software and hardware

have been introduced. The main improvements in PET technology since the SECA–1 study are commented in the following paragraphs.

Time–of–flight (TOF) technique use the difference in arrival time of two annihilation photons to more accurate determine where these actual originated. This provides images with higher SNR which improves the ability to detect small lesions with low activity that otherwise could not be distinguished from the background noise. Hence, TOF technique can improve image quality and lesion detection or decrease scan time with maintenance of image quality. In addition, TOF can be used to lower radiation dose to the patient, also giving less per–patient radionuclide costs (193, 194).

Point spread function (PSF) corrects for photon mispositioning and takes into account resolution degrading effects that influence the measured counts along the LOR like photon non–collinearity, positron range and detector related effects. These effects can either be considered during image reconstruction or post-recontruction. Coincidence counts are coupled to the activity in the different voxels. PSF leads to higher and more uniform spatial resolution (194-197).

Respiration gating. Respiratory gated (four–dimensional (4D)) PET is increasingly used in clinical work, especially in radiation planning, but also to increase sensitivity of PET in general (171, 198). During respiratory gated 4D PET, the respiration cycle is divided into several phases, and data from the different phases are added to focus on the ^{18}F–FDG uptake. Also, a 4D CT can be performed by dividing the CT into the same phases as the 4D PET to improve the attenuation correction by fusing the correct anatomic area from the CT to the corresponding ^{18}F–FDG PET-uptake throughout the respiration cycle making a 4D PET/4D CT.

Digitalization. Several vendors offer PET systems where conventional photomultiplier tubes have been replaced by photomultipliers with digital readout. Digital PET systems are able to detect single scintillation photons by incorporating electronics to achieve a (up to) one–to–one relation between the scintillator crystal elements and the digital photomultipliers. These properties provide improved spatial resolution, improved detection of small lesions and a possibility of lower radiopharmaceutical dose compared to analogue systems (194).

^{18}F–FDG PET in combination with full dose CECT instead of the standard low dose CT without contrast enhancement is also more frequently used. Several studies have shown that patients with CRC can benefit from ^{18}F–FDG PET/CECT compared to conventional ^{18}F–FDG PET/CT and could significantly affect patient management (199-201).

6.2.2 New PET tracers

Hundreds of PET tracers are available, but most of these are currently used for research purposes, and only a few of the total number of tracers are established in clinical practice. Cell proliferation and hypoxia are important elements in cancer development, and PET tracers imaging these processes are discussed in the following paragraphs.

^{18}F–3′–fluoro–3′–deoxythymidine (**^{18}F–FLT**) is a thymidine analogue that is phosphorylated by thymidine kinase, which is active during cell proliferation, and trapped intracellularly. Consequently, ^{18}F–FLT image cell proliferation in vivo and has been used as a non–invasive assessment of chemotherapy response in breast cancer (202, 203) and high grade non-Hodgkin´s lymphoma (204). In malignant lymphoma and head and neck squamous cell carcinoma, pretreatment ^{18}F–FLT MTV and ^{18}F–FLT–total lesion proliferation have shown the ability to predict prognosis (205, 206). ^{18}F–FLT has lower uptake compared to ^{18}F–FDG, however ^{18}F–FLT has shown the same potential as ^{18}F–FDG for detecting primary tumors and LN metastases (207) in CRC, but low sensitivity for detecting hepatic CRC metastases (208). A systematic review from 2016 on ^{18}F–FLT uptake as measure of treatment response in cancer patients concluded that ^{18}F–FLT seems to be a good predictor of early response to radio chemotherapy. ^{18}F–FLT uptake showed good correlation with progression–free survival and DFS. Less consistent correlation was found between ^{18}F–FLT uptake and survival. However, only a few CRC studies were included (209).

Hypoxic tumors are associated with aggressiveness, increased risk of invasion and metastases, poor prognosis, and resistance to radiation and chemotherapy. Multiple PET tracers binding to and visualizing hypoxic cells are available (210). Due to the selectivity of hypoxic tissue, ^{18}F-fluoromisonidazole (**FMISO**) is the most commonly

used tracer for hypoxia imaging. However, it has not gained acceptance in clinical routine use due to the limited traced clearance from the body and moderate ratios between hypoxic–to–normoxic tissue with moderate contrast images. The vast majority of clinical studies performed with these tracers are performed on head and neck squamous cell carcinoma and only a few on CRC (211-213).

In the patients considered for inclusion to the SECA study detection of extrahepatic CRC metastases is of vital importance to select the patients with the best possible prognosis. Even though many tracers have been available for many years, there is a lack of large clinical studies and none of these tracers currently outperform ^{18}F–FDG PET in the assessment of CRC.

6.2.3 Dynamic PET

In conventional PET imaging static images are made on the basis of typically two to three minutes uptake of a ROI. Dynamic PET (DPET) can provide information about the distribution of a tracer in a predefined VOI over time. Malignant tumors can accumulate tracers differently and benign lesions can have different kinetics compared to malignant lesions. Sixty–minute frame protocols like for example 10 frames of 30 seconds, 5 frames in 60 seconds, 5 frames in 120 seconds and 8 frames in 300 seconds can be used and uptake curves are generated (214). Added DPET to assess tracer uptake kinetics has shown improved performance compared to conventional PET in the management of oncological patients (214, 215). However, DPET is confined to research and scientific purposes because it is more time consuming and requires dedicated software. Future PET scanners will require less acquisition time and software for more advanced analysis and DPET will probably be integrated and available for clinical use.

In patients with CRC liver metastases it can be challenging to assess and report whether LNs in the liver hilum are suspicious of metastatic disease (malignant) or reactive (benign). Dynamic PET uptake of these LNs could possibly improve this assessment.

6.2.5 Texture analysis

PET image texture analysis is used to characterize heterogeneity of tumor ^{18}F–FDG uptake (216-220). Due to necrosis, hypoxia, cell proliferation and microvessel

density, the ^{18}F–FDG tumor uptake is usually not homogenous across the tumor volume (221-223). Heterogeneity has shown to be associated to impaired clinical outcome and response to therapy compared to more homogenous tumors in squamous cell head and neck cancer (224), non-small cell lung cancer (225) and esophageal cancer (220). A few small studies have evaluated ^{18}F–FDG texture analysis in CRC (226, 227) with promising results in order to predict OS and DFS. Overall, ^{18}F–FDG PET texture analysis is still considered to be a tool for research purposes only and implementation in clinical routine is still to come. However, texture analysis has a potential for adding diagnostic and prognostic value to conventional imaging.

Final message

Based on the current knowledge and the results from **Paper II** and **Paper III**, a tailored ^{18}F–FDG PET/CECT including a 4D PET/ 4D CT of the upper abdomen performed on a PET scanner with the latest technological improvements is recommended for all patients considered for LT for NCLM. The examination should be performed and assessed by dedicated nuclear medicine physicians and radiologists at the transplant unit. These available improvements in the field of imaging can most likely improve the patient selection. Furthermore, new or improved tracers, DPET and texture analysis can probably add value in the future. In line with the general trend in cancer treatment, PET protocols should also be personalized.

7. REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.
2. Kreftregistetet. Cancer in Norway 2016 2017 [20.11.17]. Available from: https://www.kreftregisteret.no/globalassets/cancer-in-norway/2016/cin-2106.pdf.
3. Dunlop MG, British Society for G, Association of Coloproctology for Great B, Ireland. Guidance on large bowel surveillance for people with two first degree relatives with colorectal cancer or one first degree relative diagnosed with colorectal cancer under 45 years. Gut. 2002;51 Suppl 5:V17-20.
4. Ferguson LR, Harris PJ. The dietary fibre debate: more food for thought. Lancet. 2003;361(9368):1487-8.
5. Research WCRFAIfC. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. 2007 [01.12.17]. Available from: http://wcrf.org/int/research-we-fund/continuous-update-project-cup/second-expert-report.
6. Research WCRFAIfC. Colorectal Cancer 2011 Report: Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. Washington DC: 2011 [01.12.17]. Available from: http://wcrf.org/sites/default/files/Colorectal-Cancer-2011-Report.pdf
7. Baglietto L, Jenkins MA, Severi G, Giles GG, Bishop DT, Boyle P, et al. Measures of familial aggregation depend on definition of family history: meta-analysis for colorectal cancer. J Clin Epidemiol. 2006;59(2):114-24.
8. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer. 2001;91(4):854-62.
9. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48(4):526-35.
10. Friedman S, Rubin PH, Bodian C, Goldstein E, Harpaz N, Present DH. Screening and surveillance colonoscopy in chronic Crohn's colitis. Gastroenterology. 2001;120(4):820-6.
11. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med. 1990;323(18):1228-33.

12. Arnold CN, Goel A, Blum HE, Boland CR. Molecular pathogenesis of colorectal cancer: implications for molecular diagnosis. Cancer. 2005;104(10):2035-47.
13. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: Pathologic aspects. J Gastrointest Oncol. 2012;3(3):153-73.
14. Organization WH. Pathology and Genetics of Tumours of the Digestive System 2000 [01.12.17]. Available from: https://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb2/BB2.pdf.
15. Cancer Genome Atlas N. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330-7.
16. Sinicrope FA, Okamoto K, Kasi PM, Kawakami H. Molecular Biomarkers in the Personalized Treatment of Colorectal Cancer. Clin Gastroenterol Hepatol. 2016;14(5):651-8.
17. Arrington AK, Heinrich EL, Lee W, Duldulao M, Patel S, Sanchez J, et al. Prognostic and predictive roles of KRAS mutation in colorectal cancer. Int J Mol Sci. 2012;13(10):12153-68.
18. Hertzman Johansson C, Egyhazi Brage S. BRAF inhibitors in cancer therapy. Pharmacol Ther. 2014;142(2):176-82.
19. Kocoglu H, Velibeyoglu FM, Karaca M, Tural D. Clinical efficacy and drug resistance of anti-epidermal growth factor receptor therapy in colorectal cancer. World J Gastrointest Oncol. 2016;8(1):1-7.
20. Kekelidze M, D'Errico L, Pansini M, Tyndall A, Hohmann J. Colorectal cancer: current imaging methods and future perspectives for the diagnosis, staging and therapeutic response evaluation. World J Gastroenterol. 2013;19(46):8502-14.
21. Pickhardt PJ. Recent developments in colorectal imaging. Current opinion in gastroenterology. 2015;31(1):76-80.
22. Dewhurst C, Rosen MP, Blake MA, Baker ME, Cash BD, Fidler JL, et al. ACR Appropriateness Criteria pretreatment staging of colorectal cancer. Journal of the American College of Radiology : JACR. 2012;9(11):775-81.
23. Smith NJ, Bees N, Barbachano Y, Norman AR, Swift RI, Brown G. Preoperative computed tomography staging of nonmetastatic colon cancer predicts outcome: implications for clinical trials. Br J Cancer. 2007;96(7):1030-6.
24. Tudyka V, Blomqvist L, Beets-Tan RG, Boelens PG, Valentini V, van de Velde CJ, et al. EURECCA consensus conference highlights about colon & rectal

cancer multidisciplinary management: the radiology experts review. Eur J Surg Oncol. 2014;40(4):469-75.
25. R P. Basic prinsiples on Computed Tomography (CT). Cardiac CT Angiography Manual Springer, London; 2015. p. 19-58.
26. Lam AK, Chan SS, Leung M. Synchronous colorectal cancer: clinical, pathological and molecular implications. World J Gastroenterol. 2014;20(22):6815-20.
27. Dighe S, Blake H, Koh MD, Swift I, Arnaout A, Temple L, et al. Accuracy of multidetector computed tomography in identifying poor prognostic factors in colonic cancer. Br J Surg. 2010;97(9):1407-15.
28. Dighe S, Purkayastha S, Swift I, Tekkis PP, Darzi A, A'Hern R, et al. Diagnostic precision of CT in local staging of colon cancers: a meta-analysis. Clin Radiol. 2010;65(9):708-19.
29. Leufkens AM, van den Bosch MA, van Leeuwen MS, Siersema PD. Diagnostic accuracy of computed tomography for colon cancer staging: a systematic review. Scand J Gastroenterol. 2011;46(7-8):887-94.
30. Muhi A, Ichikawa T, Motosugi U, Sou H, Nakajima H, Sano K, et al. Diagnosis of colorectal hepatic metastases: comparison of contrast-enhanced CT, contrast-enhanced US, superparamagnetic iron oxide-enhanced MRI, and gadoxetic acid-enhanced MRI. J Magn Reson Imaging. 2011;34(2):326-35.
31. Parnaby CN, Bailey W, Balasingam A, Beckert L, Eglinton T, Fife J, et al. Pulmonary staging in colorectal cancer: a review. Colorectal Dis. 2012;14(6):660-70.
32. Plewes DB, Kucharczyk W. Physics of MRI: a primer. J Magn Reson Imaging. 2012;35(5):1038-54.
33. Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2012;19(7):2212-23.
34. Shihab OC, Moran BJ, Heald RJ, Quirke P, Brown G. MRI staging of low rectal cancer. Eur Radiol. 2009;19(3):643-50.
35. Yu SK, Chand M, Tait DM, Brown G. Magnetic resonance imaging defined mucinous rectal carcinoma is an independent imaging biomarker for poor prognosis and poor response to preoperative chemoradiotherapy. Eur J Cancer. 2014;50(5):920-7.

36. Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology. 2003;227(2):371-7.
37. Kim JH, Beets GL, Kim MJ, Kessels AG, Beets-Tan RG. High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? Eur J Radiol. 2004;52(1):78-83.
38. Hermanek P, Merkel S, Fietkau R, Rodel C, Hohenberger W. Regional lymph node metastasis and locoregional recurrence of rectal carcinoma in the era of TME [corrected] surgery. Implications for treatment decisions. Int J Colorectal Dis. 2010;25(3):359-68.
39. D'Onofrio M, Crosara S, De Robertis R, Canestrini S, Mucelli RP. Contrast-Enhanced Ultrasound of Focal Liver Lesions. AJR Am J Roentgenol. 2015;205(1):W56-66.
40. Helsedirektoratet. Nasjonalt handlingsprogram tykk- og endetarmskreft. 2017.
41. Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology. 2004;232(3):773-83.
42. Kauer WK, Prantl L, Dittler HJ, Siewert JR. The value of endosonographic rectal carcinoma staging in routine diagnostics: a 10-year analysis. Surg Endosc. 2004;18(7):1075-8.
43. Starck M, Bohe M, Simanaitis M, Valentin L. Rectal endosonography can distinguish benign rectal lesions from invasive early rectal cancers. Colorectal Dis. 2003;5(3):246-50.
44. Kapoor V, McCook BM, Torok FS. An introduction to PET-CT imaging. Radiographics. 2004;24(2):523-43.
45. Jadvar H, Colletti PM, Delgado-Bolton R, Esposito G, Krause BJ, Iagaru AH, et al. Appropriate Use Criteria for (18)F-FDG PET/CT in Restaging and Treatment Response Assessment of Malignant Disease. J Nucl Med. 2017;58(12):2026-37.
46. Tout D, Dickson J, Bradley A. Basic Principles of PET-CT Imaging. In: Szyszko T, editor. PET/CT in Oesophageal and Gastric Cancer. Cham: Springer International Publishing; 2016. p. 31-42.

47. Kinahan PE, Fletcher JW. PET/CT Standardized Uptake Values (SUVs) in Clinical Practice and Assessing Response to Therapy. Seminars in ultrasound, CT, and MR. 2010;31(6):496-505.
48. Lameka K, Farwell MD, Ichise M. Chapter 11 - Positron Emission Tomography. In: Masdeu JC, González RG, editors. Handb Clin Neurol. 135: Elsevier; 2016. p. 209-27.
49. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50 Suppl 1:122S-50S.
50. Network NCC. 2017 [Available from: http://www.nccn.org/professionals/physician_gls/PDF/colon/rectal/.pdf.
51. Abdel-Nabi H, Doerr RJ, Lamonica DM, Cronin VR, Galantowicz PJ, Carbone GM, et al. Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. Radiology. 1998;206(3):755-60.
52. Furukawa H, Ikuma H, Seki A, Yokoe K, Yuen S, Aramaki T, et al. Positron emission tomography scanning is not superior to whole body multidetector helical computed tomography in the preoperative staging of colorectal cancer. Gut. 2006;55(7):1007-11.
53. Kantorova I, Lipska L, Belohlavek O, Visokai V, Trubac M, Schneiderova M. Routine (18)F-FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. J Nucl Med. 2003;44(11):1784-8.
54. Cipe G, Ergul N, Hasbahceci M, Firat D, Bozkurt S, Memmi N, et al. Routine use of positron-emission tomography/computed tomography for staging of primary colorectal cancer: does it affect clinical management? World J Surg Oncol. 2013;11:49.
55. Davey K, Heriot AG, Mackay J, Drummond E, Hogg A, Ngan S, et al. The impact of 18-fluorodeoxyglucose positron emission tomography-computed tomography on the staging and management of primary rectal cancer. Dis Colon Rectum. 2008;51(7):997-1003.
56. Heriot AG, Hicks RJ, Drummond EG, Keck J, Mackay J, Chen F, et al. Does positron emission tomography change management in primary rectal cancer? A prospective assessment. Dis Colon Rectum. 2004;47(4):451-8.

57. Llamas-Elvira JM, Rodriguez-Fernandez A, Gutierrez-Sainz J, Gomez-Rio M, Bellon-Guardia M, Ramos-Font C, et al. Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. Eur J Nucl Med Mol Imaging. 2007;34(6):859-67.
58. Park IJ, Kim HC, Yu CS, Ryu MH, Chang HM, Kim JH, et al. Efficacy of PET/CT in the accurate evaluation of primary colorectal carcinoma. Eur J Surg Oncol. 2006;32(9):941-7.
59. Petersen RK, Hess S, Alavi A, Hoilund-Carlsen PF. Clinical impact of FDG-PET/CT on colorectal cancer staging and treatment strategy. Am J Nucl Med Mol Imaging. 2014;4(5):471-82.
60. Vriens D, de Geus-Oei LF, van der Graaf WT, Oyen WJ. Tailoring therapy in colorectal cancer by PET-CT. Q J Nucl Med Mol Imaging. 2009;53(2):224-44.
61. Pelosi E, Deandreis D, Cassalia L, Penna D. Diagnostic Applications of Nuclear Medicine: Colorectal Cancer. In: Strauss HW, Mariani G, Volterrani D, Larson SM, editors. Nuclear Oncology: From Pathophysiology to Clinical Applications. Cham: Springer International Publishing; 2016. p. 1-21.
62. Huebner RH, Park KC, Shepherd JE, Schwimmer J, Czernin J, Phelps ME, et al. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. J Nucl Med. 2000;41(7):1177-89.
63. Lu YY, Chen JH, Chien CR, Chen WT, Tsai SC, Lin WY, et al. Use of FDG-PET or PET/CT to detect recurrent colorectal cancer in patients with elevated CEA: a systematic review and meta-analysis. Int J Colorectal Dis. 2013;28(8):1039-47.
64. Yu T, Meng N, Chi D, Zhao Y, Wang K, Luo Y. Diagnostic Value of (18)F-FDG PET/CT in Detecting Local Recurrent Colorectal Cancer: A Pooled Analysis of 26 Individual Studies. Cell Biochem Biophys. 2015;72(2):443-51.
65. Zhang C, Chen Y, Xue H, Zheng P, Tong J, Liu J, et al. Diagnostic value of FDG-PET in recurrent colorectal carcinoma: a meta-analysis. Int J Cancer. 2009;124(1):167-73.
66. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology. 2010;257(3):674-84.
67. Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L, et al. Performance of imaging modalities in diagnosis of liver metastases from colorectal

cancer: a systematic review and meta-analysis. J Magn Reson Imaging. 2010;31(1):19-31.
68. Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. Eur J Nucl Med Mol Imaging. 2015;42(1):152-63.
69. Wiering B, Krabbe PF, Jager GJ, Oyen WJ, Ruers TJ. The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases. Cancer. 2005;104(12):2658-70.
70. Moulton CA, Gu CS, Law CH, Tandan VR, Hart R, Quan D, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA. 2014;311(18):1863-9.
71. Patel K, Hadar N, Lee J, Siegel BA, Hillner BE, Lau J. The lack of evidence for PET or PET/CT surveillance of patients with treated lymphoma, colorectal cancer, and head and neck cancer: a systematic review. J Nucl Med. 2013;54(9):1518-27.
72. Brush J BK, Chappell F, et al. The Value of FDG Positron Emission Tomography/Computerised Tomography (PET/CT) in Pre-Operative Staging of Colorectal Cancer: A Systematic Review and Economic Evaluation: Southampton (UK): NIHR Journals Library; 2011 Sep. (Health Technology Assessment, No. 15.35.) 2011.
73. Maffione AM, Marzola MC, Capirci C, Colletti PM, Rubello D. Value of (18)F-FDG PET for Predicting Response to Neoadjuvant Therapy in Rectal Cancer: Systematic Review and Meta-Analysis. AJR Am J Roentgenol. 2015;204(6):1261-8.
74. Memon S, Lynch AC, Akhurst T, Ngan SY, Warrier SK, Michael M, et al. Systematic review of FDG-PET prediction of complete pathological response and survival in rectal cancer. Ann Surg Oncol. 2014;21(11):3598-607.
75. Rymer B, Curtis NJ, Siddiqui MR, Chand M. FDG PET/CT Can Assess the Response of Locally Advanced Rectal Cancer to Neoadjuvant Chemoradiotherapy: Evidence From Meta-analysis and Systematic Review. Clin Nucl Med. 2016;41(5):371-5.
76. Zhang C, Tong J, Sun X, Liu J, Wang Y, Huang G. 18F-FDG-PET evaluation of treatment response to neo-adjuvant therapy in patients with locally advanced rectal cancer: a meta-analysis. Int J Cancer. 2012;131(11):2604-11.

77. de Jong EA, ten Berge JC, Dwarkasing RS, Rijkers AP, van Eijck CH. The accuracy of MRI, endorectal ultrasonography, and computed tomography in predicting the response of locally advanced rectal cancer after preoperative therapy: A metaanalysis. Surgery. 2016;159(3):688-99.
78. Memon S, Lynch AC, Bressel M, Wise AG, Heriot AG. Systematic review and meta-analysis of the accuracy of MRI and endorectal ultrasound in the restaging and response assessment of rectal cancer following neoadjuvant therapy. Colorectal Dis. 2015;17(9):748-61.
79. Wu LM, Zhu J, Hu J, Yin Y, Gu HY, Hua J, et al. Is there a benefit in using magnetic resonance imaging in the prediction of preoperative neoadjuvant therapy response in locally advanced rectal cancer? Int J Colorectal Dis. 2013;28(9):1225-38.
80. Li YL, Wu LM, Chen XX, Delproposto Z, Hu JN, Xu JR. Is diffusion-weighted MRI superior to FDG-PET or FDG-PET/CT in evaluating and predicting pathological response to preoperative neoadjuvant therapy in patients with rectal cancer? J Dig Dis. 2014;15(10):525-37.
81. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis. 2009;11(4):354-64; discussion 64-5.
82. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol. 2010;28(2):272-8.
83. West NP, Morris EJ, Rotimi O, Cairns A, Finan PJ, Quirke P. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet Oncol. 2008;9(9):857-65.
84. Smith AJ, Driman DK, Spithoff K, Hunter A, McLeod RS, Simunovic M, et al. Guideline for optimization of colorectal cancer surgery and pathology. J Surg Oncol. 2010;101(1):5-12.
85. Berger AC, Sigurdson ER, LeVoyer T, Hanlon A, Mayer RJ, Macdonald JS, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol. 2005;23(34):8706-12.

86. Kim JC, Lee KH, Yu CS, Kim HC, Kim JR, Chang HM, et al. The clinicopathological significance of inferior mesenteric lymph node metastasis in colorectal cancer. Eur J Surg Oncol. 2004;30(3):271-9.
87. Rosenberg R, Friederichs J, Schuster T, Gertler R, Maak M, Becker K, et al. Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single-center analysis of 3,026 patients over a 25-year time period. Ann Surg. 2008;248(6):968-78.
88. Guren MG, Korner H, Pfeffer F, Myklebust TA, Eriksen MT, Edna TH, et al. Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010. Acta Oncol. 2015;54(10):1714-22.
89. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg. 1982;69(10):613-6.
90. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638-46.
91. Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336(14):980-7.
92. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011;12(6):575-82.
93. Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. 2008;26(22):3687-94.
94. Glimelius B, Gronberg H, Jarhult J, Wallgren A, Cavallin-Stahl E. A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol. 2003;42(5-6):476-92.
95. Larsen SG, Wiig JN, Emblemsvaag HL, Groholt KK, Hole KH, Bentsen A, et al. Extended total mesorectal excision in locally advanced rectal cancer (T4a) and the clinical role of MRI-evaluated neo-adjuvant downstaging. Colorectal Dis. 2009;11(7):759-67.
96. Eriksen MT, Wibe A, Syse A, Haffner J, Wiig JN. Inadvertent perforation during rectal cancer resection in Norway. Br J Surg. 2004;91(2):210-6.

97. Quan D, Gallinger S, Nhan C, Auer RA, Biagi JJ, Fletcher GG, et al. The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review. Surgery. 2012;151(6):860-70.
98. Soreide JA, Eiriksson K, Sandvik O, Viste A, Horn A, Johnsen G, et al. [Surgical treatment of liver metastases from colorectal cancer]. Tidsskr Nor Laegeforen. 2008;128(1):50-3.
99. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg. 2004;240(3):438-47; discussion 47-50.
100. Primrose JN. Surgery for colorectal liver metastases. Br J Cancer. 2010;102(9):1313-8.
101. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer. 2006;94(7):982-99.
102. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol. 2012;4:283-301.
103. Bonanni L, De'liguori Carino N, Deshpande R, Ammori BJ, Sherlock DJ, Valle JW, et al. A comparison of diagnostic imaging modalities for colorectal liver metastases. Eur J Surg Oncol. 2014;40(5):545-50.
104. Sahani DV, Bajwa MA, Andrabi Y, Bajpai S, Cusack JC. Current status of imaging and emerging techniques to evaluate liver metastases from colorectal carcinoma. Ann Surg. 2014;259(5):861-72.
105. Selzner M, Hany TF, Wildbrett P, McCormack L, Kadry Z, Clavien PA. Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? Ann Surg. 2004;240(6):1027-34; discussion 35-6.
106. Adam R. Colorectal cancer with synchronous liver metastases. Br J Surg. 2007;94(2):129-31.
107. Sorbye H, Pfeiffer P, Cavalli-Bjorkman N, Qvortrup C, Holsen MH, Wentzel-Larsen T, et al. Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients. Cancer. 2009;115(20):4679-87.

108. Lim HJ, Fitzgerald C, Gill S, Melosky B, Speers C, Barnett J, et al. Impact of irinotecan and oxaliplatin on overall survival in patients with metastatic colorectal cancer (MCRC): A population- based study. J Clin Oncol. 2007;25(18_suppl):4077-.
109. Meulenbeld HJ, van Steenbergen LN, Janssen-Heijnen MLG, Lemmens VEPP, Creemers GJ. Significant improvement in survival of patients presenting with metastatic colon cancer in the south of The Netherlands from 1990 to 2004. Ann Oncol. 2008;19(9):1600-4.
110. Glimelius B, Ristamaki R, Kjaer M, Pfeiffer P, Skovsgaard T, Tveit KM, et al. Irinotecan combined with bolus 5-fluorouracil and folinic acid Nordic schedule as first-line therapy in advanced colorectal cancer. Ann Oncol. 2002;13(12):1868-73.
111. Glimelius B, Sorbye H, Balteskard L, Bystrom P, Pfeiffer P, Tveit K, et al. A randomized phase III multicenter trial comparing irinotecan in combination with the Nordic bolus 5-FU and folinic acid schedule or the bolus/infused de Gramont schedule (Lv5FU2) in patients with metastatic colorectal cancer. Ann Oncol. 2008;19(5):909-14.
112. Sorbye H, Glimelius B, Berglund A, Fokstuen T, Tveit KM, Braendengen M, et al. Multicenter phase II study of Nordic fluorouracil and folinic acid bolus schedule combined with oxaliplatin as first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2004;22(1):31-8.
113. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359(17):1757-65.
114. Price TJ, Peeters M, Kim TW, Li J, Cascinu S, Ruff P, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol. 2014;15(6):569-79.
115. Boeckx N, Koukakis R, Op de Beeck K, Rolfo C, Van Camp G, Siena S, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. Ann Oncol. 2017;28(8):1862-8.
116. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in

patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28(31):4697-705.
117. Dueland S, Guren TK, Hagness M, Glimelius B, Line PD, Pfeiffer P, et al. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? Ann Surg. 2015;261(5):956-60.
118. Masi G, Vasile E, Loupakis F, Cupini S, Fornaro L, Baldi G, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. J Natl Cancer Inst. 2011;103(1):21-30.
119. Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol. 2011;29(15):2011-9.
120. Stang A, Fischbach R, Teichmann W, Bokemeyer C, Braumann D. A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. Eur J Cancer. 2009;45(10):1748-56.
121. Lee EW, Thakor AS, Tafti BA, Liu DM. Y90 selective internal radiation therapy. Surg Oncol Clin N Am. 2015;24(1):167-85.
122. Scorsetti M, Comito T, Tozzi A, Navarria P, Fogliata A, Clerici E, et al. Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. J Cancer Res Clin Oncol. 2015;141(3):543-53.
123. Massmann A, Rodt T, Marquardt S, Seidel R, Thomas K, Wacker F, et al. Transarterial chemoembolization (TACE) for colorectal liver metastases--current status and critical review. Langenbecks Arch Surg. 2015;400(6):641-59.
124. Shirouzu K, Isomoto H, Hayashi A, Nagamatsu Y, Kakegawa T. Surgical treatment for patients with pulmonary metastases after resection of primary colorectal carcinoma. Cancer. 1995;76(3):393-8.
125. Internullo E, Cassivi SD, Van Raemdonck D, Friedel G, Treasure T. Pulmonary metastasectomy: a survey of current practice amongst members of the European Society of Thoracic Surgeons. J Thorac Oncol. 2008;3(11):1257-66.
126. Thomford NR, Woolner LB, Clagett OT. THE SURGICAL TREATMENT OF METASTATIC TUMORS IN THE LUNGS. J Thorac Cardiovasc Surg. 1965;49:357-63.
127. Erhunmwunsee L, Tong BC. Preoperative Evaluation and Indications for Pulmonary Metastasectomy. Thorac Surg Clin. 2016;26(1):7-12.

128. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg. 2007;84(1):324-38.
129. McCormack PM, Burt ME, Bains MS, Martini N, Rusch VW, Ginsberg RJ. Lung resection for colorectal metastases. 10-year results. Arch Surg. 1992;127(12):1403-6.
130. Dickinson KJ, Blackmon SH. Results of Pulmonary Resection: Colorectal Carcinoma. Thorac Surg Clin. 2016;26(1):41-7.
131. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? J Hepatol. 2007;47(4):460-6.
132. Le Treut YP, Gregoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J, et al. Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. Ann Surg. 2013;257(5):807-15.
133. Rosenau J, Bahr MJ, von Wasielewski R, Mengel M, Schmidt HH, Nashan B, et al. Ki67, E-cadherin, and p53 as prognostic indicators of long-term outcome after liver transplantation for metastatic neuroendocrine tumors. Transplantation. 2002;73(3):386-94.
134. Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. Transpl Int. 2008;21(12):1107-17.
135. Registry ELT. European Liver Transplant Registry 2017 Available from: http://www.eltr.org
136. Uskudar O, Raja K, Schiano TD, Fiel MI, del Rio Martin J, Chang C. Liver Transplantation Is Possible in Some Patients with Liver Metastasis of Colon Cancer. Transplant Proc. 2011;43(5):2070-4.
137. Kocman B, Mikulić D, Jadrijevic S, Poljak M, Kocman I, Gašparov S, et al. Long-Term Survival After Living-Donor Liver Transplantation for Unresectable Colorectal Metastases to the Liver: Case Report. Transplant Proc. 2011;43(10):4013-5.
138. Foss A, Adam R, Dueland S. Liver transplantation for colorectal liver metastases: revisiting the concept. Transpl Int. 2010;23(7):679-85.
139. Fosby B, Melum E, Bjoro K, Bennet W, Rasmussen A, Andersen IM, et al. Liver transplantation in the Nordic countries - An intention to treat and post-

transplant analysis from The Nordic Liver Transplant Registry 1982-2013. Scand J Gastroenterol. 2015;50(6):797-808.
140. Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. Cold Spring Harb Perspect Med. 2013;3(7).
141. Piselli P, Serraino D, Segoloni GP, Sandrini S, Piredda GB, Scolari MP, et al. Risk of de novo cancers after transplantation: results from a cohort of 7217 kidney transplant recipients, Italy 1997-2009. Eur J Cancer. 2013;49(2):336-44.
142. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol. 2006;6(10):715-27.
143. Munz C, Moormann A. Immune escape by Epstein-Barr virus associated malignancies. Semin Cancer Biol. 2008;18(6):381-7.
144. O'Donovan P, Perrett CM, Zhang X, Montaner B, Xu YZ, Harwood CA, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science. 2005;309(5742):1871-4.
145. Engels EA, Pfeiffer RM, Fraumeni JF, Jr., Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891-901.
146. McCaughan GW, Vajdic CM. De novo malignant disease after liver transplantation? Risk and surveillance strategies. Liver Transpl. 2013;19 Suppl 2:S62-7.
147. Mukthinuthalapati PK, Gotur R, Ghabril M. Incidence, risk factors and outcomes of de novo malignancies post liver transplantation. World J Hepatol. 2016;8(12):533-44.
148. Vivarelli M, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. Ann Surg. 2008;248(5):857-62.
149. Sint Nicolaas J, de Jonge V, Steyerberg EW, Kuipers EJ, van Leerdam ME, Veldhuyzen-van Zanten SJ. Risk of colorectal carcinoma in post-liver transplant patients: a systematic review and meta-analysis. Am J Transplant. 2010;10(4):868-76.
150. Jorgensen KK, Lindstrom L, Cvancarova M, Castedal M, Friman S, Schrumpf E, et al. Colorectal neoplasia in patients with primary sclerosing cholangitis undergoing liver transplantation: a Nordic multicenter study. Scand J Gastroenterol. 2012;47(8-9):1021-9.

151. Herrero JI, Alegre F, Quiroga J, Pardo F, Inarrairaegui M, Sangro B, et al. Usefulness of a program of neoplasia surveillance in liver transplantation. A preliminary report. Clin Transplant. 2009;23(4):532-6.
152. Johnson EE, Leverson GE, Pirsch JD, Heise CP. A 30-year analysis of colorectal adenocarcinoma in transplant recipients and proposal for altered screening. J Gastrointest Surg. 2007;11(3):272-9.
153. Buell JF, Papaconstantinou HT, Skalow B, Hanaway MJ, Alloway RR, Woodle ES. De novo colorectal cancer: five-year survival is markedly lower in transplant recipients compared with the general population. Transplant Proc. 2005;37(2):960-1.
154. Verran DJ, Mulhearn MH, Dilworth PJ, Balderson GA, Munn S, Chen JW, et al. Nature and outcomes of the increased incidence of colorectal malignancy after liver transplantation in Australasia. Med J Aust. 2013;199(9):610-2.
155. Fung J, Kelly D, Kadry Z, Patel-Tom K, Eghtesad B. Immunosuppression in liver transplantation: beyond calcineurin inhibitors. Liver Transpl. 2005;11(3):267-80.
156. Atkins MB, Hidalgo M, Stadler WM, Logan TF, Dutcher JP, Hudes GR, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. J Clin Oncol. 2004;22(5):909-18.
157. Chan S, Scheulen ME, Johnston S, Mross K, Cardoso F, Dittrich C, et al. Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. J Clin Oncol. 2005;23(23):5314-22.
158. Wolf S, Hoffmann VS, Habicht A, Kauke T, Bucher J, Schoenberg M, et al. Effects of mTOR-Is on malignancy and survival following renal transplantation: A systematic review and meta-analysis of randomized trials with a minimum follow-up of 24 months. PLoS One. 2018;13(4):e0194975.
159. Geissler EK, Schnitzbauer AA, Zulke C, Lamby PE, Proneth A, Duvoux C, et al. Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial. Transplantation. 2016;100(1):116-25.

160. Hagness M, Foss A, Line PD, Scholz T, Jorgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257(5):800-6.
161. Hagness M, Foss A, Egge TS, Dueland S. Patterns of recurrence after liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg Oncol. 2014;21(4):1323-9.
162. Acuna SA, Huang JW, Daly C, Shah PS, Kim SJ, Baxter NN. Outcomes of Solid Organ Transplant Recipients With Preexisting Malignancies in Remission: A Systematic Review and Meta-Analysis. Transplantation. 2016.
163. Schwartz M. A biomathematical approach to clinical tumor growth. Cancer. 1961;14:1272-94.
164. Nakamura T, Matsumine A, Matsubara T, Asanuma K, Uchida A, Sudo A. Clinical impact of the tumor volume doubling time on sarcoma patients with lung metastases. Clin Exp Metastasis. 2011;28(8):819-25.
165. Kim EY, Lee JI, Sung YM, Cho SH, Shin DB, Kim YS, et al. Pulmonary metastases from colorectal cancer: imaging findings and growth rates at follow-up CT. Clin Imaging. 2012;36(1):14-8.
166. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
167. Laird AK. Dynamics of Tumor Growth. Br J Cancer. 1964;18:490.
168. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. Philos Trans Royal Soc London. 1825;115:pp. 513-83.
169. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42(2):328-54.
170. Pettinato C, Nanni C, Farsad M, Castellucci P, Sarnelli A, Civollani S, et al. Artefacts of PET/CT images. Biomedical Imaging and Intervention Journal. 2006;2(4):e60.
171. Chi A, Nguyen NP. 4D PET/CT as a Strategy to Reduce Respiratory Motion Artifacts in FDG-PET/CT. Front Oncol. 2014;4:205.
172. van der Vos CS, Koopman D, Rijnsdorp S, Arends AJ, Boellaard R, van Dalen JA, et al. Quantification, improvement, and harmonization of small lesion

detection with state-of-the-art PET. Eur J Nucl Med Mol Imaging. 2017;44(Suppl 1):4-16.
173. Akhurst T, Kates TJ, Mazumdar M, Yeung H, Riedel ER, Burt BM, et al. Recent chemotherapy reduces the sensitivity of [18F]fluorodeoxyglucose positron emission tomography in the detection of colorectal metastases. J Clin Oncol. 2005;23(34):8713-6.
174. Bains SJ, Mahic M, Myklebust TA, Smastuen MC, Yaqub S, Dorum LM, et al. Aspirin As Secondary Prevention in Patients With Colorectal Cancer: An Unselected Population-Based Study. J Clin Oncol. 2016;34(21):2501-8.
175. Geissler EK, Schlitt HJ, Thomas G. mTOR, cancer and transplantation. Am J Transplant. 2008;8(11):2212-8.
176. Kim YI, Paeng JC, Cheon GJ, Suh KS, Lee DS, Chung JK, et al. Prediction of Posttransplantation Recurrence of Hepatocellular Carcinoma Using Metabolic and Volumetric Indices of 18F-FDG PET/CT. J Nucl Med. 2016;57(7):1045-51.
177. Bailly M, Venel Y, Orain I, Salame E, Ribeiro MJ. 18F-FDG PET in Liver Transplantation Setting of Hepatocellular Carcinoma: Predicting Histology? Clin Nucl Med. 2016;41(3):e126-9.
178. Detry O, Govaerts L, Deroover A, Vandermeulen M, Meurisse N, Malenga S, et al. Prognostic value of (18)F-FDG PET/CT in liver transplantation for hepatocarcinoma. World J Gastroenterol. 2015;21(10):3049-54.
179. Lee SD, Kim SH, Kim YK, Kim C, Kim SK, Han SS, et al. (18)F-FDG-PET/CT predicts early tumor recurrence in living donor liver transplantation for hepatocellular carcinoma. Transpl Int. 2013;26(1):50-60.
180. Lin CY, Liao CW, Chu LY, Yen KY, Jeng LB, Hsu CN, et al. Predictive Value of 18F-FDG PET/CT for Vascular Invasion in Patients With Hepatocellular Carcinoma Before Liver Transplantation. Clin Nucl Med. 2017;42(4):e183-e7.
181. Fendler WP, Philippe Tiega DB, Ilhan H, Paprottka PM, Heinemann V, Jakobs TF, et al. Validation of several SUV-based parameters derived from 18F-FDG PET for prediction of survival after SIRT of hepatic metastases from colorectal cancer. J Nucl Med. 2013;54(8):1202-8.
182. Soydal C, Kucuk ON, Gecim EI, Bilgic S, Elhan AH. The prognostic value of quantitative parameters of 18F-FDG PET/CT in the evaluation of response to internal radiation therapy with yttrium-90 in patients with liver metastases of colorectal cancer. Nucl Med Commun. 2013;34(5):501-6.

183. Zerizer I, Al-Nahhas A, Towey D, Tait P, Ariff B, Wasan H, et al. The role of early (1)(8)F-FDG PET/CT in prediction of progression-free survival after (9)(0)Y radioembolization: comparison with RECIST and tumour density criteria. Eur J Nucl Med Mol Imaging. 2012;39(9):1391-9.
184. Shady W, Kishore S, Gavane S, Do RK, Osborne JR, Ulaner GA, et al. Metabolic tumor volume and total lesion glycolysis on FDG-PET/CT can predict overall survival after (90)Y radioembolization of colorectal liver metastases: A comparison with SUVmax, SUVpeak, and RECIST 1.0. Eur J Radiol. 2016;85(6):1224-31.
185. Dueland S, Hagness M, Line PD, Guren TK, Tveit KM, Foss A. Is Liver Transplantation an Option in Colorectal Cancer Patients with Nonresectable Liver Metastases and Progression on All Lines of Standard Chemotherapy? Ann Surg Oncol. 2015;22(7):2195-200.
186. Andersen MH, Dueland S, Hagness M, Vidnes T, Finstad ED, Wahl AK, et al. Quality of life following liver transplantation in patients with liver metastases from colorectal carcinoma. Scand J Caring Sci. 2012;26(4):713-9.
187. Bjørnelv GW, Dueland S, Line P, Joranger P, Fretland Å, Edwin B, et al. PCN161 - The Cost-Effectiveness of Liver Transplantation Compared To Chemotherapy for Non-Resectable Liver-Only Metastases After Colorectal Cancer (MCRC). Value Health. 2017;20(9):A441.
188. Bjørnelv GMW, Dueland S, Line P-D, Joranger P, Fretland ÅA, Edwin B, et al. Cost-effectiveness of liver transplantation in patients with colorectal metastases confined to the liver. BJS.0(0).
189. Grut H, Revheim ME, Line PD, Dueland S. Importance of 18F-FDG PET/CT to select patients with nonresectable colorectal liver metastases for liver transplantation. Nucl Med Commun. 2018.
190. Vodkin I, Kuo A. Extended Criteria Donors in Liver Transplantation. Clin Liver Dis. 2017;21(2):289-301.
191. Dueland S, Foss A, Solheim JM, Hagness M, Line PD. Survival following liver transplantation for liver-only colorectal metastases compared with hepatocellular carcinoma. Br J Surg. 2018;105(6):736-42.
192. Line PD, Hagness M, Berstad AE, Foss A, Dueland S. A Novel Concept for Partial Liver Transplantation in Nonresectable Colorectal Liver Metastases: The RAPID Concept. Ann Surg. 2015;262(1):e5-9.

193. Basu S, Kwee TC, Surti S, Akin EA, Yoo D, Alavi A. Fundamentals of PET and PET/CT imaging. Ann N Y Acad Sci. 2011;1228:1-18.
194. van der Vos CS, Koopman D, Rijnsdorp S, Arends AJ, Boellaard R, van Dalen JA, et al. Quantification, improvement, and harmonization of small lesion detection with state-of-the-art PET. Eur J Nucl Med Mol Imaging. 2017;44(Suppl 1):4-16.
195. Rogasch JMM, Steffen IG, Hofheinz F, Großer OS, Furth C, Mohnike K, et al. The association of tumor-to-background ratios and SUVmax deviations related to point spread function and time-of-flight F18-FDG-PET/CT reconstruction in colorectal liver metastases. EJNMMI Research. 2015;5:31.
196. Akamatsu G, Ishikawa K, Mitsumoto K, Taniguchi T, Ohya N, Baba S, et al. Improvement in PET/CT image quality with a combination of point-spread function and time-of-flight in relation to reconstruction parameters. J Nucl Med. 2012;53(11):1716-22.
197. Bellevre D, Blanc Fournier C, Switsers O, Dugué AE, Levy C, Allouache D, et al. Staging the axilla in breast cancer patients with 18F-FDG PET: how small are the metastases that we can detect with new generation clinical PET systems? Eur J Nucl Med Mol Imaging. 2014;41(6):1103-12.
198. Crivellaro C, De Ponti E, Elisei F, Morzenti S, Picchio M, Bettinardi V, et al. Added diagnostic value of respiratory-gated 4D 18F-FDG PET/CT in the detection of liver lesions: a multicenter study. Eur J Nucl Med Mol Imaging. 2017.
199. Dirisamer A, Halpern BS, Flory D, Wolf F, Beheshti M, Mayerhoefer ME, et al. Performance of integrated FDG-PET/contrast-enhanced CT in the staging and restaging of colorectal cancer: comparison with PET and enhanced CT. Eur J Radiol. 2010;73(2):324-8.
200. Morbelli S, Conzi R, Campus C, Cittadini G, Bossert I, Massollo M, et al. Contrast-enhanced [18 F] fluorodeoxyglucose-positron emission tomography/computed tomography in clinical oncology: tumor-, site-, and question-based comparison with standard positron emission tomography/computed tomography. Cancer Imaging. 2014;14:10.
201. Soyka JD, Veit-Haibach P, Strobel K, Breitenstein S, Tschopp A, Mende KA, et al. Staging pathways in recurrent colorectal carcinoma: is contrast-enhanced 18F-FDG PET/CT the diagnostic tool of choice? J Nucl Med. 2008;49(3):354-61.

202. Pio BS, Park CK, Pietras R, Hsueh WA, Satyamurthy N, Pegram MD, et al. Usefulness of 3'-[F-18]fluoro-3'-deoxythymidine with positron emission tomography in predicting breast cancer response to therapy. Mol Imaging Biol. 2006;8(1):36-42.
203. Kenny L, Coombes RC, Vigushin DM, Al-Nahhas A, Shousha S, Aboagye EO. Imaging early changes in proliferation at 1 week post chemotherapy: a pilot study in breast cancer patients with 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography. Eur J Nucl Med Mol Imaging. 2007;34(9):1339-47.
204. Herrmann K, Wieder HA, Buck AK, Schoffel M, Krause BJ, Fend F, et al. Early response assessment using 3'-deoxy-3'-[18F]fluorothymidine-positron emission tomography in high-grade non-Hodgkin's lymphoma. Clin Cancer Res. 2007;13(12):3552-8.
205. Herrmann K, Buck AK, Schuster T, Junger A, Wieder HA, Graf N, et al. Predictive value of initial 18F-FLT uptake in patients with aggressive non-Hodgkin lymphoma receiving R-CHOP treatment. J Nucl Med. 2011;52(5):690-6.
206. Hoshikawa H, Mori T, Yamamoto Y, Kishino T, Fukumura T, Samukawa Y, et al. Prognostic value comparison between (18)F-FLT PET/CT and (18)F-FDG PET/CT volume-based metabolic parameters in patients with head and neck cancer. Clin Nucl Med. 2015;40(6):464-8.
207. Nakajo M, Nakajo M, Kajiya Y, Jinguji M, Nishimata N, Shimaoka S, et al. Diagnostic performance of (1)(8)F-fluorothymidine PET/CT for primary colorectal cancer and its lymph node metastasis: comparison with (1)(8)F-fluorodeoxyglucose PET/CT. Eur J Nucl Med Mol Imaging. 2013;40(8):1223-32.
208. Francis DL, Visvikis D, Costa DC, Arulampalam TH, Townsend C, Luthra SK, et al. Potential impact of [18F]3'-deoxy-3'-fluorothymidine versus [18F]fluoro-2-deoxy-D-glucose in positron emission tomography for colorectal cancer. Eur J Nucl Med Mol Imaging. 2003;30(7):988-94.
209. Bollineni VR, Kramer GM, Jansma EP, Liu Y, Oyen WJ. A systematic review on [(18)F]FLT-PET uptake as a measure of treatment response in cancer patients. Eur J Cancer. 2016;55:81-97.
210. Fleming IN, Manavaki R, Blower PJ, West C, Williams KJ, Harris AL, et al. Imaging tumour hypoxia with positron emission tomography. Br J Cancer. 2014;112:238.
211. Havelund BM, Holdgaard PC, Rafaelsen SR, Mortensen LS, Theil J, Bender D, et al. Tumour hypoxia imaging with 18F-fluoroazomycinarabinofuranoside

PET/CT in patients with locally advanced rectal cancer. Nucl Med Commun. 2013;34(2):155-61.
212. Roels S, Slagmolen P, Nuyts J, Lee JA, Loeckx D, Maes F, et al. Biological image-guided radiotherapy in rectal cancer: is there a role for FMISO or FLT, next to FDG? Acta Oncol. 2008;47(7):1237-48.
213. Dietz DW, Dehdashti F, Grigsby PW, Malyapa RS, Myerson RJ, Picus J, et al. Tumor hypoxia detected by positron emission tomography with 60Cu-ATSM as a predictor of response and survival in patients undergoing Neoadjuvant chemoradiotherapy for rectal carcinoma: a pilot study. Dis Colon Rectum. 2008;51(11):1641-8.
214. Dimitrakopoulou-Strauss A, Hoffmann M, Bergner R, Uppenkamp M, Haberkorn U, Strauss LG. Prediction of progression-free survival in patients with multiple myeloma following anthracycline-based chemotherapy based on dynamic FDG-PET. Clin Nucl Med. 2009;34(9):576-84.
215. Dimitrakopoulou-Strauss A, Strauss LG, Egerer G, Vasamiliette J, Mechtersheimer G, Schmitt T, et al. Impact of dynamic 18F-FDG PET on the early prediction of therapy outcome in patients with high-risk soft-tissue sarcomas after neoadjuvant chemotherapy: a feasibility study. J Nucl Med. 2010;51(4):551-8.
216. Cook GJ, O'Brien ME, Siddique M, Chicklore S, Loi HY, Sharma B, et al. Non-Small Cell Lung Cancer Treated with Erlotinib: Heterogeneity of (18)F-FDG Uptake at PET-Association with Treatment Response and Prognosis. Radiology. 2015;276(3):883-93.
217. El Naqa I, Grigsby PW, Apte A, Kidd E, Donnelly E, Khullar D, et al. Exploring feature-based approaches in PET images for predicting cancer treatment outcomes. Pattern Recognition. 2009;42(6):1162-71.
218. Hyun SH, Kim HS, Choi SH, Choi DW, Lee JK, Lee KH, et al. Intratumoral heterogeneity of (18)F-FDG uptake predicts survival in patients with pancreatic ductal adenocarcinoma. Eur J Nucl Med Mol Imaging. 2016;43(8):1461-8.
219. Lee HS, Oh JS, Park YS, Jang SJ, Choi IS, Ryu JS. Differentiating the grades of thymic epithelial tumor malignancy using textural features of intratumoral heterogeneity via (18)F-FDG PET/CT. Ann Nucl Med. 2016;30(4):309-19.
220. Nakajo M, Jinguji M, Nakabeppu Y, Nakajo M, Higashi R, Fukukura Y, et al. Texture analysis of (18)F-FDG PET/CT to predict tumour response and prognosis

of patients with esophageal cancer treated by chemoradiotherapy. Eur J Nucl Med Mol Imaging. 2017;44(2):206-14.
221. Pugachev A, Ruan S, Carlin S, Larson SM, Campa J, Ling CC, et al. Dependence of FDG uptake on tumor microenvironment. Int J Radiat Oncol Biol Phys. 2005;62(2):545-53.
222. van Baardwijk A, Bosmans G, van Suylen RJ, van Kroonenburgh M, Hochstenbag M, Geskes G, et al. Correlation of intra-tumour heterogeneity on 18F-FDG PET with pathologic features in non-small cell lung cancer: a feasibility study. Radiother Oncol. 2008;87(1):55-8.
223. van Velden FH, Cheebsumon P, Yaqub M, Smit EF, Hoekstra OS, Lammertsma AA, et al. Evaluation of a cumulative SUV-volume histogram method for parameterizing heterogeneous intratumoural FDG uptake in non-small cell lung cancer PET studies. Eur J Nucl Med Mol Imaging. 2011;38(9):1636-47.
224. Cheng NM, Fang YH, Chang JT, Huang CG, Tsan DL, Ng SH, et al. Textural features of pretreatment 18F-FDG PET/CT images: prognostic significance in patients with advanced T-stage oropharyngeal squamous cell carcinoma. J Nucl Med. 2013;54(10):1703-9.
225. Cook GJ, Yip C, Siddique M, Goh V, Chicklore S, Roy A, et al. Are pretreatment 18F-FDG PET tumor textural features in non-small cell lung cancer associated with response and survival after chemoradiotherapy? J Nucl Med. 2013;54(1):19-26.
226. Bundschuh RA, Dinges J, Neumann L, Seyfried M, Zsoter N, Papp L, et al. Textural Parameters of Tumor Heterogeneity in (1)(8)F-FDG PET/CT for Therapy Response Assessment and Prognosis in Patients with Locally Advanced Rectal Cancer. J Nucl Med. 2014;55(6):891-7.
227. Nakajo M, Kajiya Y, Tani A, Jinguji M, Nakajo M, Kitazono M, et al. A pilot study for texture analysis of (18)F-FDG and (18)F-FLT-PET/CT to predict tumor recurrence of patients with colorectal cancer who received surgery. Eur J Nucl Med Mol Imaging. 2017;44(13):2158-68.

8. PAPERS

I

Original article

Growth rates of pulmonary metastases after liver transplantation for unresectable colorectal liver metastases

H. Grut[1,6], S. Solberg[3,6], T. Seierstad[1], M. E. Revheim[1,6], T. S. Egge[1], S. G. Larsen[2], P. D. Line[4,6] and S. Dueland[5]

[1]Division of Radiology and Nuclear Medicine, and Departments of [2]Gastroenterological Surgery, [3]Thoracic Surgery, [4]Transplantation Medicine and [5]Oncology, Oslo University Hospital, and [6]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Correspondence to: Mr H. Grut, Division of Radiology and Nuclear Medicine, Oslo University Hospital, PO Box 4950 Nydalen, 0424 Oslo, Norway (e-mail: harald.grut@gmail.com)

Background: **The previously reported SECA study demonstrated a dramatic 5-year survival improvement in patients with unresectable colorectal liver metastases (CLM) treated with liver transplantation (LT) compared with chemotherapy. The objective of this study was to assess whether immunosuppressive therapy accelerates the growth of pulmonary metastases in patients transplanted for unresectable CLM.**

Methods: **Chest CT scans from 11 patients in the SECA study resected for 18 pulmonary metastases were reviewed retrospectively. Tumour diameter, volume and CT characteristics were registered and tumour volume doubling time was calculated. Findings in the SECA group were compared with those of a control group consisting of 12 patients with non-transplanted rectal cancer resected for 26 pulmonary metastases. Disease-free survival (DFS) and overall survival (OS) after first pulmonary resection were determined.**

Results: **Median doubling time based on tumour diameter and volume in the SECA and control groups were 125 and 130 days ($P = 0{\cdot}658$) and 110 and 129 days ($P = 0{\cdot}632$) respectively. The metastases in both groups were distributed to all lung lobes and were mostly peripheral. Median DFS after LT in the SECA group and after primary pelvic surgery in the control group was 17 (range 6–42) and 18 (2–57) months respectively ($P = 0{\cdot}532$). In the SECA group, estimated 5-year DFS and OS rates after first pulmonary resection were 39 and 51 per cent respectively.**

Conclusion: **Patients treated by LT for unresectable CLM have a good prognosis following resection of pulmonary metastases. Doubling time did not appear to be worse with the immunosuppression used after LT.**

Paper accepted 23 June 2017

Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10651

Introduction

About 50 per cent of patients with colorectal cancer (CRC) will develop metastases. The liver is the most frequent organ of relapse, followed by the lungs. Only 20 per cent of patients with metastatic disease are candidates for liver resection. Liver transplantation (LT) is standard treatment in patients with end-stage liver failure, and is currently also offered to selected patients with primary liver cancers such as hepatocellular carcinoma, hilar cholangiocarcinoma and liver metastases from neuroendocrine tumours[1–6]. LT for malignant tumours comprises 16 per cent of all liver transplants in the European Liver Transplant Registry[7]. Organ transplantation requires lifelong immunosuppression, which may increase the risk of *de novo* malignancy[8].

In the SECA (secondary cancer) study, 5-year survival was improved in patients with unresectable colorectal liver metastases (CLM) treated with LT compared with chemotherapy alone, with a 5-year overall survival (OS) rate of 56 *versus* 9 per cent respectively[9]. The majority of patients with CRC who underwent LT had a relapse, in the lung in two-thirds of cases[10]. Patients with pulmonary first-site recurrence had a 5-year survival rate of 72 per cent[10]. In patients with CRC who had a liver transplant the 5-year OS rate after relapse was 53 per cent[10,11]. This contrasts with patients starting first-line chemotherapy,

© 2017 BJS Society Ltd
Published by John Wiley & Sons Ltd

Table 1 Patient and baseline characteristics

	SECA group ($n = 11$)	Control group ($n = 12$)	P‡
Age at primary surgery (years)*	54 (44–64)	61 (49–74)	0·081
Age at first pulmonary resection (years)*	56 (45–67)	63 (51–76)	0·069
Sex ratio (M : F)	8 : 3	7 : 5	
Time from LT/primary surgery to pulmonary metastasis diameter ≥ 10 mm (months)*	17 (6–42)	18 (2–57)	0·532
Site of primary tumour			
Colon	6	0	
Rectum	5	12	
Timing of liver metastases			
Metachronous	3		
Synchronous	8		
KRAS status			
Wild-type	6		
Mutated	5		
No. of metastases			
5–10	9		
> 20	2		
Diameter of largest metastasis (cm)†			
< 5	7		
5–10	4		
Chemotherapy			
Lines before LT			
1	5		
2	3		
3	3		
Agent recieved before LT			
Irinotecan	7		
Oxaliplatin	10		
EGFR antibody treatment	5		
Sirolimus, before first pulmonary resection			
Dose (mg/day)*	4 (2–5)		
Plasma level (μg/l)*	11·8 (6·0–16·5)		

*Values are median (range). †Largest diameter measured at CT before liver transplantation (LT) or examination of explanted liver. EGFR, epidermal growth factor receptor. ‡Mann–Whitney U test.

of whom about 5 per cent were alive at 5 years owing to progressive disease.

The present study assessed whether immunosuppressive therapy accelerated the growth of pulmonary metastases in patients following LT.

Methods

The study group consisted of 11 patients from the SECA study who had a total of 18 pulmonary metastases resected after LT for unresectable CLM. At time of resection, these patients had only pulmonary metastases. They received immunosuppressive treatment according to the study protocol, which comprised induction with basiliximab (an interleukin-2 receptor antibody) and subsequent

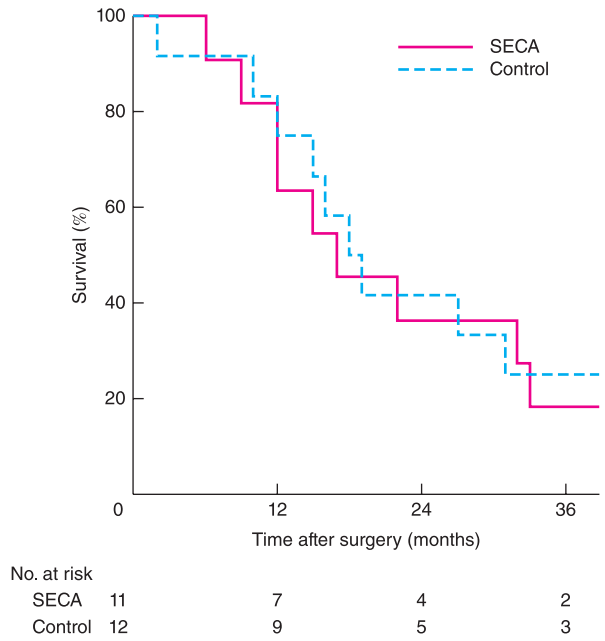

Fig. 1 Kaplan–Meier curves of disease-free survival (time to pulmonary metastasis of 10 mm or more) after liver transplantation in the SECA group and primary surgery in the control group. $P = 0·532$ (log rank test)

maintenance with an immunosuppressive regimen containing sirolimus (a mammalian target of rapamycin (mTOR) inhibitor), mycophenolate mofetil (an inosin monophosphate dehydrogenase inhibitor) and corticosteroids. Corticosteroid treatment was tapered to zero over the course of the first 6–12 months after surgery[11]. All patients from the SECA study also received acetylsalicylic acid (aspirin) to prevent thrombosis in the hepatic artery following LT.

The control group was from a prospectively registered institutional rectal cancer database and consisted of 12 patients with locally advanced rectal cancer without metastases at the time of diagnosis/primary surgical treatment. They all received chemoradiotherapy of 2 Gy × 25, with concurrent capecitabine (825 mg/m^2 twice daily) during 5 weeks of radiotherapy. After surgery for the rectal tumour, all patients in the control group developed only pulmonary metastases. No patient in the SECA group or the control group was treated with chemotherapy between LT/pelvic surgery and the detection of pulmonary metastases, or between detection of pulmonary metastases and pulmonary resection.

Institutional review board and national regional ethics committee (S-05409) approval was obtained for the project. The SECA study was registered at ClinicalTrials.gov (NCT01311453).

© 2017 BJS Society Ltd
Published by John Wiley & Sons Ltd

Table 2 Characteristics of the pulmonary metastases

	SECA group ($n = 11$)	Control group ($n = 12$)	P‡
No. of pulmonary metastases	18	26	
Diameter (RECIST) (mm)*			
At detection (first CT)	6 (5–13)	9 (5–16)	0·026
At last CT before pulmonary resection	13 (9–21)	15 (8–20)	0·623
Tumour volume (mm^3)*			
At detection (first CT)	102 (37–604)	216 (16–1375)	0·021
At last CT before resection	750 (262–2569)	818 (120–1731)	0·685
Tumour volume DT (days)*			
Diameter-based	125 (27–430)	110 (30–320)	0·658
Volume-based	130 (35–282)	129 (40–274)	0·632
Time from first to last CT (days)*	260 (84–1085)	154 (76–651)	0·094
Time from last CT to pulmonary resection (days)*	55 (2–280)	71 (7–177)	0·094
Histological postresection diameter (mm)*	15 (5–23)	15 (8–30)	0·503
Time from suspected lesion to resection (days)*	311 (132–1169)	257 (122–667)	0·277
Follow-up after LT/primary surgery (months)*	71 (24–114)	111 (77–159)	0·003
Follow-up after first resection (months)*	48 (6–95)	76 (45–144)	0·010
CEA level at first pulmonary resection (μg/l)*†	2·5 (1·2–4·8)	2·2 (< 1 to 15·0)	0·566
Characteristics of pulmonary metastases			
Distribution			
Right upper lobe	2	5	
Right middle lobe	3	3	
Right lower lobe	3	5	
Left upper lobe	7	9	
Left lower lobe	3	4	
Location			
Peripheral	18	24	
Central	0	2	
Border			
Well defined	17	21	
Spiculated	1	5	
Shape			
Round/oval	12	19	
Lobulated	6	7	
No. of metastases included			
1	7	4	
2	3	5	
3	0	1	
4	0	1	
5	1	1	

*Values are median (range). †Carcinoembryonic antigen (CEA) values of less than 1·0 μg/l were treated as 1·0 μg/l in the statistical analysis. RECIST, Response Evaluation Criteria in Solid Tumours; LT, liver transplantation. ‡Mann–Whitney *U* test.

Chest CT review

CT was performed on different scanners as part of follow-up, either at the transplantation centre or at local hospitals. According to the study protocol, the SECA group had undergone CT of the thorax every 3 months in the first year, every 6 months in the second year, and once a year in years 3–10 after transplantation. Patients in the control group were followed at the same intervals until 5 years after surgery for metastases. Thickness of slices was 2·5–3·0 mm in both groups. All CT scans were imported into a Siemens syngo.via workstation (version VB10A; Siemens, Erlangen, Germany) and reviewed retrospectively by two radiologists. The largest diameter (Response Evaluation Criteria in Solid Tumours, RECIST) and tumour volumes were obtained by using a built-in semiautomated function. The measurements were manually controlled and adjusted if needed. Tumour volume doubling time (DT), based on diameter and tumour volume for individual metastases, was calculated using the Schwartz equation[12]:

$$\mathrm{DT}\ (\text{diameter}) = (T_{\text{last CT}} - T_{\text{first CT}}) \times \frac{\log 2}{3 \times \log \frac{D_{\text{first CT}}}{D_{\text{last CT}}}}$$

$$\mathrm{DT}\ (\text{volume}) = (T_{\text{last CT}} - T_{\text{first CT}}) \times \frac{\log 2}{\log V_{\text{last CT}} - \log V_{\text{first CT}}}$$

where $T_{\text{last CT}} - T_{\text{first CT}}$ is the time between the CT scan that detected the metastasis and the last CT scan before

© 2017 BJS Society Ltd
Published by John Wiley & Sons Ltd

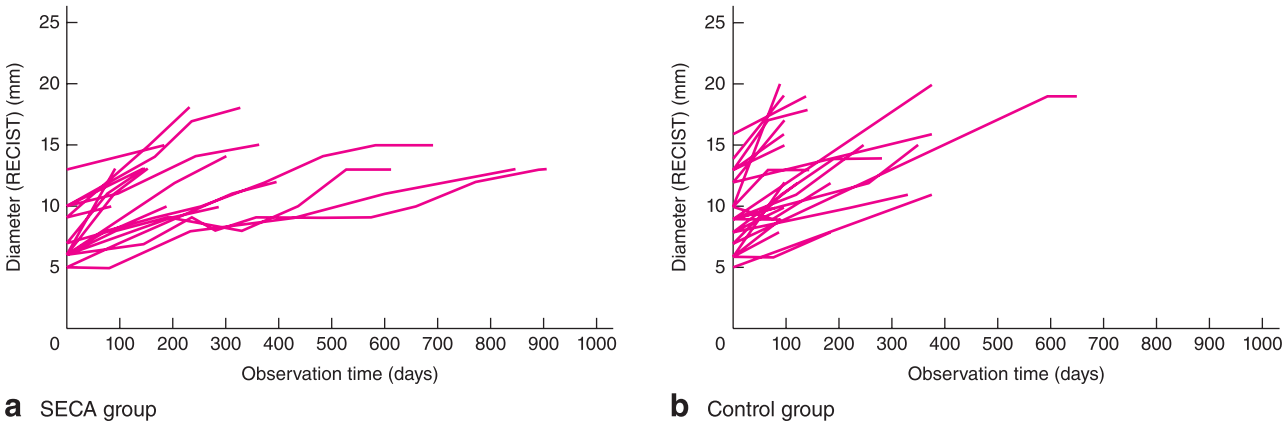

Fig. 2 Diameter (Response Evaluation Criteria in Solid Tumours, RECIST) of individual pulmonary metastases over time during follow-up in **a** the SECA group and **b** the control group

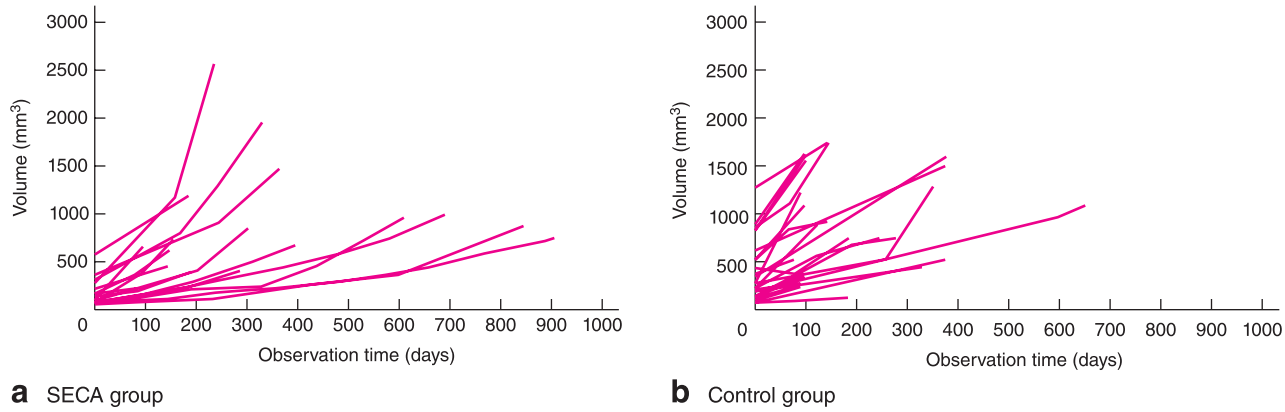

Fig. 3 Tumour volume of individual pulmonary metastases over time during follow-up in **a** the SECA group and **b** the control group

resection, $V_{last\ CT}$ and $V_{first\ CT}$ are the tumour volumes, and $D_{last\ T}$ and $D_{first\ CT}$ are the tumour diameter at these two time points.

Statistical analysis

Statistical analyses were performed with SPSS® version 24 (IBM, Armonk, New York, USA). DTs in SECA and control groups were visualized by a box plot. Several patients had more than one metastasis. Analyses were performed by considering the metastases as independent parameters. Groups of data were compared using the non-parametric Mann–Whitney *U* test and Spearman rank correlation coefficient. Survival data were estimated by means of the Kaplan–Meier method and compared with the log rank test. $P < 0{\cdot}050$ was considered statistically significant.

Results

Patient and baseline characteristics are summarized in *Table 1*. Median age at first pulmonary resection was 56 (range 45–67) years in the 11 patients in the SECA group and 63 (51–76) years in the 12 control patients ($P = 0{\cdot}069$). Median sirolimus dose was 4 (range 2–5) mg/day, and median sirolimus serum concentration was 11·8 (range 6·0–16·5) μg/l before the first pulmonary resection. In the SECA group, the dose of aspirin was 75 mg/day after LT, except in one patient who received 160 mg daily. Median (range) follow-up was 71 (24–114) months after LT in the SECA group and 111 (77–159) months after pelvic surgery in the control group. The 12 patients in the control group had surgical resection of 26 pulmonary metastases from rectal cancer between June 2004 and November 2011.

Disease-free survival after liver transplantation or primary pelvic surgery

Disease-free survival (DFS) was defined as the time from LT (SECA group) or primary pelvic surgery (control group) to CT-detected pulmonary metastases of at least 10 mm in diameter. Median (range) DFS in the SECA

© 2017 BJS Society Ltd
Published by John Wiley & Sons Ltd

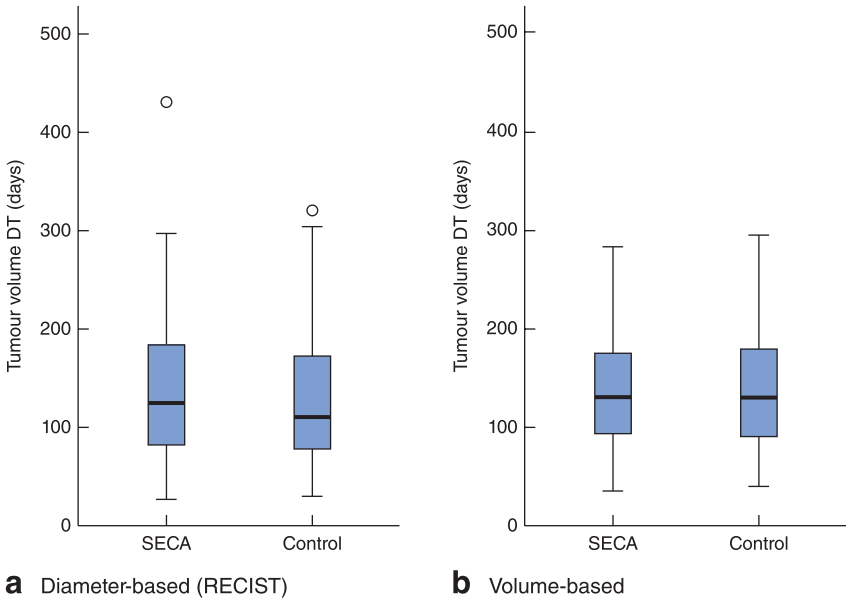

Fig. 4 Box plot of tumour volume doubling time (DT) in the SECA and control groups based on **a** tumour diameter and **b** tumour volume. Median values, interquartile ranges and ranges (excluding outliers, ○), are denoted by horizontal bars, boxes and error bars respectively. **a** $P = 0{\cdot}658$, **b** $P = 0{\cdot}632$ (Mann–Whitney U test)

and control groups was 17 (6–42) and 18 (2–57) months respectively ($P = 0{\cdot}532$). DFS rates at 1, 3 and 5 years were 64, 18 and 0 per cent after LT, compared with 75, 25 and 0 per cent after pelvic surgery in the control group (*Fig. 1*).

CT intervals and tumour size

There was no time difference from final CT to resection of pulmonary metastases between the two groups (*Table 2*). Median metastatic tumour diameter at detection was larger in the control group, but similar at pulmonary resection; the increase in tumour diameter (RECIST) with time for individual metastases is shown in *Fig. 2*. Median tumour volume at detection was smaller in the SECA group, but similar at the time of pulmonary resection (*Table 2*); the increase in tumour volume with time for individual metastases is shown in *Fig. 3*. At histological examination, the median (range) diameter of resected pulmonary metastases was 15 (5–23) mm in the SECA group and 15 (8–30) mm in the control group ($P = 0{\cdot}503$). Tumour volume at the last CT before pulmonary resection ($V_{last\ CT}$) was correlated with the diameter observed at histological examination after resection (correlation coefficient 0·78, $P < 0{\cdot}001$).

Tumour doubling times

The median (range) DT by diameter was 125 (27–430) days in the SECA group and 110 (30–320) days in the control group ($P = 0{\cdot}658$). DT of the metastases by volume was also similar (*Fig. 4*).

CT characteristics and distribution

Metastases in both groups were distributed to all lung lobes and were mostly peripheral. In the SECA group, 17 of the 18 metastases were well defined compared with 21 of 26 in the control group. CT characteristics and the distribution of the pulmonary metastases in the two groups are summarized in *Table 2*.

Recurrence and survival after resection of pulmonary metastases

Eight patients in the SECA group had a single pulmonary resection, two patients had two separate resections, and one patient has undergone resection seven times and is alive with no evidence of disease almost 10 years after LT and 8 years after the first pulmonary resection. Four of the patients developed extrapulmonary relapse. Estimated 5-year DFS and OS rate from first pulmonary resection in the SECA group was 39 and 51 per cent respectively.

In the control group, eight patients had one, three patients had two, and one patient had three pulmonary resections. In addition to the four patients who relapsed with resectable pulmonary metastases, three patients had a relapse after the first pulmonary resection. One patient

© 2017 BJS Society Ltd
Published by John Wiley & Sons Ltd

developed multiple pulmonary metastases, another had a pulmonary relapse and received stereotactic radiotherapy, and one patient developed a rhabdomyosarcoma.

There was no difference between the two groups in DFS ($P = 0{\cdot}478$) or OS ($P = 0{\cdot}084$) after first pulmonary resection. The numbers at risk are too small to present in a meaningful Kaplan–Meier curve.

Discussion

These results suggest that immunosuppression after LT for unresectable CLM does not accelerate growth of pulmonary metastases. *De novo* cancers as well as cancer recurrence may be promoted by immunosuppression owing to various mechanisms, including decreased immunosurveillance[8,13,14], facilitated action of oncogenic viruses[15] and direct alteration of DNA[16]. A meta-analysis[17] reported that pretransplant malignancy was associated with an increased risk of all-cause and cancer-specific mortality, and of developing *de novo* malignancies after transplantation compared with rates in patients without pretransplant malignancy.

It has been suggested that *de novo* malignancy after transplantation is diagnosed at younger age than in the general population and may behave more aggressively[18–21]. Despite the heavy immunosuppressive drug combinations used in the SECA study, increased growth rates of the pulmonary metastases were not observed. There was no relation between plasma sirolimus concentration and DFS or growth rates of pulmonary metastases in the SECA group (data not shown). The immunosuppressive regimen used in the SECA study contained mycophenolate mofetil, which has been reported[22] to reduce the risk of CRC development compared with ciclosporin–azathioprine immunosuppression. mTOR inhibitors have shown antiproliferative properties[23], with increased response and OS rates in patients with breast cancer and kidney cancer[24,25].

According to the SECA study protocol, all patients received aspirin to prevent arterial thrombosis. A recent Norwegian study[26] of 23 162 patients showed that aspirin use after diagnosis of CRC was independently associated with improved CRC-specific survival and OS. The protocol-specified aspirin use may inhibit the growth of pulmonary metastases, but this is not yet known.

The present study has some limitations, including its retrospective design and the fact that different CT scanners and scan protocols were used. However, two dedicated radiologists reassessed all metastases to achieve consensus, and CT-determined volume correlated with histological findings. The number of metastases included in the study was small. Only patients with resectable pulmonary metastases that were confirmed histologically as CRC metastases were included in this study. In general, it is difficult to find an ideal control group to compare with liver-transplanted patients. Patients in the control group had a lower tumour burden at the time of pelvic surgery compared with the tumour burden at LT in the SECA group, and had received less chemotherapy. It is likely that the control group had a more favourable tumour biology compared with that of the transplanted group, yet immunosuppression did not adversely impact tumour progression in the transplanted group. The size of the pulmonary metastases at detection was larger in the control group, but similar at the time of pulmonary resection. It is conceivable that this represented a selection bias, whereby DTs were faster in the control group, artificially improving times in the SECA group. This does not detract from the simple message that LT is possible for CLM, with no discernable negative influence on disease activity, on the basis of this small, retrospective, lung-focused study.

Acknowledgements

This work was supported by Oslo University Hospital and the Norwegian Cancer Society.
Disclosure: The authors declare no conflict of interest.

References

1 Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. *Transpl Int* 2008; **21**: 1107–1117.
2 Le Treut YP, Grégoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J *et al.* Liver transplantation for neuroendocrine tumors in Europe – results and trends in patient selection: a 213-case European Liver Transplant Registry study. *Ann Surg* 2013; **257**: 807–815.
3 Masuoka HC, Rosen CB. Transplantation for cholangiocarcinoma. *Clin Liver Dis* 2011; **15**: 699–715.
4 Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L *et al.*; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35–43.
5 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693–699.
6 Lee KK, Kim DG, Moon IS, Lee MD, Park JH. Liver transplantation *versus* liver resection for the treatment of hepatocellular carcinoma. *J Surg Oncol* 2010; **101**: 47–53.
7 European Liver Transplant Registry. http://www.eltr.org [accessed 1 March 2017].

© 2017 BJS Society Ltd
Published by John Wiley & Sons Ltd

8 Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. *Cold Spring Harb Perspect Med* 2013; **3**: pii.
9 Dueland S, Guren TK, Hagness M, Glimelius B, Line PD, Pfeiffer P *et al.* Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? *Ann Surg* 2015; **261**: 956–960.
10 Hagness M, Foss A, Egge TS, Dueland S. Patterns of recurrence after liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg Oncol* 2014; **21**: 1323–1329.
11 Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B *et al.* Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg* 2013; **257**: 800–806.
12 Schwartz M. A biomathematical approach to clinical tumor growth. *Cancer* 1961; **14**: 1272–1294.
13 Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. *Nat Rev Immunol* 2006; **6**: 715–727.
14 Piselli P, Serraino D, Segoloni GP, Sandrini S, Piredda GB, Scolari MP *et al.*; Immunosuppression and Cancer Study Group. Risk of *de novo* cancers after transplantation: results from a cohort of 7217 kidney transplant recipients, Italy 1997–2009. *Eur J Cancer* 2013; **49**: 336–344.
15 Münz C, Moormann A. Immune escape by Epstein–Barr virus associated malignancies. *Semin Cancer Biol* 2008; **18**: 381–387.
16 O'Donovan P, Perrett CM, Zhang X, Montaner B, Xu YZ, Harwood CA *et al.* Azathioprine and UVA light generate mutagenic oxidative DNA damage. *Science* 2005; **309**: 1871–1874.
17 Acuna SA, Huang JW, Daly C, Shah PS, Kim SJ, Baxter NN. Outcomes of solid organ transplant recipients with preexisting malignancies in remission: a systematic review and meta-analysis. *Transplantation* 2017; **101**: 471–481.
18 Mukthinuthalapati PK, Gotur R, Ghabril M. Incidence, risk factors and outcomes of *de novo* malignancies post liver transplantation. *World J Hepatol* 2016; **8**: 533–544.
19 Buell JF, Papaconstantinou HT, Skalow B, Hanaway MJ, Alloway RR, Woodle ES. *De novo* colorectal cancer: five-year survival is markedly lower in transplant recipients compared with the general population. *Transplant Proc* 2005; **37**: 960–961.
20 Johnson EE, Leverson GE, Pirsch JD, Heise CP. A 30-year analysis of colorectal adenocarcinoma in transplant recipients and proposal for altered screening. *J Gastrointest Surg* 2007; **11**: 272–279.
21 Verran DJ, Mulhearn MH, Dilworth PJ, Balderson GA, Munn S, Chen JW *et al.* Nature and outcomes of the increased incidence of colorectal malignancy after liver transplantation in Australasia. *Med J Aust* 2013; **199**: 610–612.
22 Safaeian M, Robbins HA, Berndt SI, Lynch CF, Fraumeni JF Jr, Engels EA. Risk of colorectal cancer after solid organ transplantation in the United States. *Am J Transplant* 2016; **16**: 960–967.
23 Geissler EK, Schlitt HJ, Thomas G. mTOR, cancer and transplantation. *Am J Transplant* 2008; **8**: 2212–2218.
24 Atkins MB, Hidalgo M, Stadler WM, Logan TF, Dutcher JP, Hudes GR *et al.* Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004; **22**: 909–918.
25 Chan S, Scheulen ME, Johnston S, Mross K, Cardoso F, Dittrich C *et al.* Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. *J Clin Oncol* 2005; **23**: 5314–5322.
26 Bains SJ, Mahic M, Myklebust TA, Smastuen MC, Yaqub S, Dorum LM *et al.* Aspirin as secondary prevention in patients with colorectal cancer: an unselected population-based study. *J Clin Oncol* 2016; **34**: 2501–2508.

© 2017 BJS Society Ltd
Published by John Wiley & Sons Ltd

II

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-017-3843-9

ORIGINAL ARTICLE

The prognostic value of ^{18}F–FDG PET/CT prior to liver transplantation for nonresectable colorectal liver metastases

Harald Grut[1,2] · **Svein Dueland**[3] · **Pål Dag Line**[2,4] · **Mona Elisabeth Revheim**[1,2]

Received: 28 July 2017 / Accepted: 26 September 2017
© Springer-Verlag GmbH Germany 2017

Abstract
Purpose The main objective of this study was to evaluate the prognostic value of volumetric and metabolic information derivied from F-18 fluorodeoxyglucose positron emission tomography (^{18}F–FDG PET) in combination with computed tomography (CT) prior to liver transplantation (LT) in patients with nonresectable colorectal liver metastases (CLM). Due to scarcity of liver grafts, prognostic information enabling selection of candidates who will gain the highest survival after LT is of vital importance. ^{18}F–FDG PET/CT was a part of the preoperative study protocol. Patients without evidence of extrahepatic malignant disease on ^{18}F–FDG PET/CT who also fulfilled all the other inclusion criteria underwent LT.
Methods The preoperative ^{18}F–FDG PET/CT examinations of all patients included in the SECA (secondary cancer) study were retrospectively assessed. Maximum, mean and peak standardized uptake values (SUV_{max}, SUV_{mean} and SUV_{peak}), tumor to background (T/B) ratio, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were measured and calculated for all liver metastases. Total MTV and TLG were calculated for each patient. Cut-off values were determined for each of these parameters by using receiver operating characteristic (ROC) analysis dividing the patients into two groups. One, three and five-year overall survival (OS) and disease free survival (DFS) for patients over and under the cut-off value were compared by using the Kaplan–Meier method and log rank test.
Results Twenty-three patients underwent LT in the SECA study. Total MTV and TLG under the cut-off values were significantly correlated to improved OS at three and five years ($p = 0.027$ and 0.026) and DFS ($p = 0.01$). One, three and five-year OS and DFS were not significantly related to SUV_{max}, SUV_{mean}, SUV_{peak} or T/B-ratio.
Conclusion Total MTV and TLG from ^{18}F FDG PET/CT prior to LT for nonresectable CLM were significantly correlated to improved three and five-year OS and DFS and can potentially improve the patient selection for LT.

Keywords ^{18}F-FDG PET/CT · Colorectal cancer · Liver transplantation · Liver metastases

✉ Harald Grut
harald.grut@gmail.com

1 Division of Radiology and Nuclear Medicine, Oslo University Hospital, P.o.box 4950, Nydalen, 0424 Oslo, Norway

2 Institute of Clinical Medicine, University of Oslo, Oslo, Norway

3 Division of Oncology, Oslo University Hospital, Oslo, Norway

4 Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway

Introduction

Liver metastases occur in approximately half of the patients with colorectal cancer (CRC). Liver resection is currently the only potentially curative treatment option in colorectal liver metastases (CLM) with a reported five-year survival of about 40% [1]. However, only up to 20% of the patients with liver metastases are candidates for curative liver resection [1].

Liver transplantation (LT) is established as a treatment option for some primary liver cancers like hepatocellular carcinoma (HCC) and cholangiocarsinoma (CCA) [2–5]. The most common secondary carcinoma that are considered for LT is metastases from neuroendocrine tumors [6, 7].

In the previously reported SECA (secondary cancer) study we showed an increase in 5-year overall survival (OS) in patients treated with LT for nonresectable CLM (56%) compared to chemotherapy (9%), which is the standard treatment option

Published online: 12 October 2017

[8]. Shortness of liver donors precludes more general utilization of LT in nonresectable CLM. Thus, optimized patient selection is crucial for providing liver grafts to recipients that will benefit most from the procedure.

F-18 fluorodeoxyglucose positron emission tomography in combination with computed tomography (^{18}F–FDG PET/CT) is widely used in oncology and well established in the assessment of recurrent and residual CRC, including the evaluation of CLM, and prior to potentially curative metastasectomy [9–11]. ^{18}F–FDG PET as routine in the initial staging of colon and rectal cancer is still controversial and not established [10]. However, current guidelines from the National Comprehensive Cancer Network (NCCN) recommend a staging ^{18}F–FDG PET examination for patients with potentially surgically curable metastatic colorectal cancer [11]. PET has been shown to have high sensitivity and specificity in detecting liver metastases [12, 13], and ^{18}F–FDG PET/CT outperforms contrast enhanced CT in detection of extra-hepatic metastases [14]. Thus, ^{18}F–FDG PET/CT could possibly provide additional information about N and M stage as a part of the primary staging of colorectal cancer [15]. ^{18}F–FDG activity is most commonly quantified by measuring standardized uptake values (SUV) in a volume of interest (VOI). SUV is a semiquantitative measure representing the concentration of FDG within the VOI normalized to the injected radioactivity per unit body weight and corrected for physical decay [16]. High SUVs are associated with high metabolic activity and aggressiveness, and also in patients with CLM [17, 18]. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are metabolic-based volumetric parameters that can be obtained by using a threshold to delineate lesion activity relative to the background [19]. MTV and TLG have shown to provide prognostic information in several cancers including esophageal cancer [20, 21], non-small cell lung cancer [22–24] and head and neck cancer [25, 26]. Only a limited number of CRC studies have correlated MTV and TLG measurements to clinical outcome [27–30].

The main objective of this study was to report the prognostic value of the volumetric and metabolic information derived from ^{18}F–FDG PET/CT prior to LT for nonresectable CLM to evaluate whether this might improve patient selection.

Methods

Patients

The liver metastases from ^{18}F–FDG PET/CT scans of 23 patients who underwent LT for nonresectable CLM (SECA study) were retrospectively assessed. In the SECA study, ^{18}F–FDG PET/CT scan was a part of the preoperative study protocol. Patients who fulfilled all inclusion criteria without evidence of extrahepatic malignant disease on ^{18}F–FDG PET/CT were included [8]. The inclusion period of the SECA study was from November 2006 to April 2012, and the ^{18}F–FDG PET/CT scans were performed in the same period of time prior to the transplantation. Chemotherapy was not given the last 4–6 weeks before the ^{18}F–FDG PET/CT scan.

^{18}F–FDG PET/CT procedure

All ^{18}F–FDG PET/CT procedures were performed on a hybrid PET/CT system (Siemens Biograph 64 or Siemens Biograph 16), Siemens Medical Systems, Erlangen, Germany. The patients fasted for six hours and serum glucose levels were assessed immediately before ^{18}F–FDG was injected intravenously. Median (range) injected dose was 390 MBq (336–424). Image acquisition started after 1 h relaxed rest in a separate room. A standard whole body (WB) PET examination from skull base to the upper thigh with an acquisition time of 3 min per bed position and 30% overlap was performed. The PET examination was reconstructed with the image format recommended by the scanner manufacturer for use in daily routine of 168 × 168 pixels (pixel size 4.06 mm) using OSEM with four iterations and eight subsets (4i/8 s) and a Gaussian post-reconstruction filter that had full-widths at half maximum (FWHM) to equal 5 mm. A low-dose CT study without contrast was used for anatomical information and attenuation correction of the WB-PET study. The CT acquisition parameters were: 120 kV, approximately 50mAs (AEC), and axial slices of 3 mm.

Image assessments

All ^{18}F–FDG PET/CT scans were evaluated by one experienced nuclear medicine physician and one experienced radiologist by consensus (MER and HG). Maximum standardized uptake value (SUV_{max}), average SUV (SUV_{mean}), peak SUV (SUV_{peak}), tumor to background ratio (T/B-ratio), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of the liver metastases were measured and registered by using a Siemens SyngoVia workstation (version VB10A, Erlangen, Germany). $SUV_{max,}$ SUV_{mean} and SUV_{peak}, were measured by manually placing a volume of interest (VOI) over target lesions. In patients with more than one liver metastasis, the highest value of SUV_{max} and SUV_{mean} was registered. SUV_{peak} was defined as the SUV_{mean} of the volume of 1 cm^3 around the SUV_{max}. MTV (cm^3) was defined as the tumor volume with ^{18}F–FDG uptake segmented by fixed threshold methods at 40% of SUV_{max} in the VOI. Cross-sectional regions were displayed in axial, sagittal and coronal projections. TLG was calculated by multiplying SUV_{mean} by MTV. Total MTV and TLG were calculated by adding the values from all metastases for each patient. Liver background was measured by placing a region of interest (ROI) of 3 cm in the right liver lobe according to the PERCIST criteria [31]. $SUV_{max,}$ SUV_{mean} and SUV_{peak} were registered if the uptake

Table 1 Patients and baseline characteristics

Patients, n	23
Age at liver transplantation (LT), years, median (range)	54 (44–64)
Time from ^{18}F FDG PET/CT to LT, days, median (range)	70 (12–293)
Gender	
Male, n (%)	13 (57)
Female, n (%)	10 (43)
Primary tumor, n (%)	
Colon	13 (57)
Rectum	10 (43)
Time of liver metastases	
Syncronous, n (%)	19 (83)
Metacronous, n (%)	4 (17)
Lines of chemotherapy before liver transplantation, n (%)	
1	10 (43)
2	9 (40)
3	4 (17)
Progressive disease at liver transplantation, n (%) [a]	
Yes	15 (65)
No	8 (35)

[a] Increased size of liver metastases and/or increased carcinoembryonic antigen (CEA)

of the liver metastases was higher than the mean liver background uptake × 1.5 + standard deviation of the liver background × 2 (PERCIST cuf-off value) [31]. If we were not able to delineate the liver metastases from the liver background, MTV and TLG were given a value of 0.

Statistical analysis

Statistical analyses were performed with SPSS (IBM, version 24, Chicago, IL, USA). Cut-off values of SUV_{max}, SUV_{mean}, SUV_{peak}, total MTV, total TLG and T/B-ratio were determined by using receiver operating characteristic (ROC) curves. Area under curve (AUC) was calculated, and the optimal cut-off value for each variable was defined as the value with the highest combined sensitivity and specificity. The patients were divided into two groups based on the cut-off value for each of these factors. OS and disease free survival (DFS) curves were generated by using the Kaplan–Meier method, and the groups were compared by using the log rank test. Two–sided *P*-values <0.05 were considered statistically significant.

Results

Patients and baseline characteristics

Patient and baseline characteristics are summarized in Table 1. Median (range) age at LT was 54 (44–64) years and 57% were men. Median (range) time interval between the FDG PET/CT scan and LT was 70 (12–293) days.

Volumetric and metabolic measurements

Median and range of SUV_{max}, SUV_{mean}, SUV_{peak}, total MTV, total TLG and T/B-ratio measurements and calculations are summarized in Table 2. Cut-off values based on the ROC analysis were calculated for SUV_{max} (7.88 g/cm^3), SUV_{mean} (4.28 g/cm^3), SUV_{peak} (5.68 g/cm^3), total MTV (69.81cm^3), total TLG (256,70 g) and T/B-ratio (4.06).

Overall survival analysis

The OS analysis is summarized in Table 3. All patients were observed for five years or until death. One, three and five-year OS Kaplan Meier analysis and log rank test that compared the patients over and under the determined cut-off values for SUV_{max}, SUV_{mean}, SUV_{peak}, total MTV, total TLG and T/B-ratio were performed (Fig. 1). Patients with MTV and TLG under cut-off had three and five-year OS of 90.9% and 63.6% compared to the patients over cut-off who had three and five-year OS of 50.0% and 25%, respectively (P = 0.027 and 0.026). SUV_{max}, SUV_{mean}, SUV_{peak} and T/B-ratio were not significantly correlated to OS. Figure 2 illustrates one patient with low total MTV and TLG and high SUVs and T/B-ratio still alive ten years after LT and one patient with high total MTV and TLG who died only two years after LT.

Table 2 Results

	All	Cut-off	Under cut-off	Over cut-off
SUV_{max} (g/cm^3), median (range)	9.02 (2.33–21.5)	7.88	3.74 (2.33–8.67)	13.1 (8.88–21.5)
SUV_{mean} (g/cm^3), median (range)	5.13 (1.62–12.3)	4.28	2.15 (1.62–3.76)	7.43 (5.12–13.1)
SUV_{peak} (g/cm^3), median (range)	7.34 (1.92–17.5)	5.68	2.90 (1.92–5.41)	11.2 (5.95–17.5)
MTV (cm^3), median (range)	98.5 (0–874.1)	69.8	0 (0–41.1)	172.2 (98.5–874.1)
TLG (g), median (range)	302.1 (0–4437.5)	256.7	0 (0–211.3)	1294.0 (302.14–4437.5)
T/B-ratio, median (range)	5.3 (1.00–11.1)	4.06	1.48 (1.00–5.26)	6.35 (5.29–11.1)

Table 3 Survival after liver transplantation

	Follow up time (years)	Survival (%)		P-value
		Over cut-off	Under cut-off	
SUV_{max}	1	92.3	100	0.380
	3	61.5	80.0	0.263
	5	38.5	50.0	0.308
SUV_{mean}	1	92.9	100	0.423
	3	64.3	77.8	0.392
	5	35.7	55.6	0.260
SUV_{peak}	1	92.9	100	0.423
	3	64.3	77.8	0.392
	5	35.7	55.6	0.260
MTV	1	91.7	100	0.338
	3	50.0	90.9	**0.027**
	5	25.0	63.6	**0.026**
TLG	1	91.7	100	0.338
	3	50.0	90.9	**0.027**
	5	25.0	63.6	**0.026**
T/B-ratio	1	90.9	100	0.296
	3	54.5	83.3	0.091
	5	36.4	50.0	0.207

Disease free survival analysis

All SECA patients developed recurrent disease, and the lungs were most affected. Median (range) disease free survival (DFS) was 11 (2–39) months for all patients. Median (range) DFS for the patients under and over the cut-off for MTV and TLG was 5 (2–15) and 12 (3–39) months ($P = 0.01$), respectively. *P*-values for SUV_{max}, SUV_{mean}, SUV_{peak} and T/B-ratio were 0.07, 0.08, 0.08 and 0.05, respectively. DFS Kaplan Meier curve for MTV and TLG is shown in Fig. 3.

Discussion

Our results show that low values of total MTV and TLG on the preoperative ^{18}F–FDG PET/CT is significantly correlated to increased three and five-year OS and DFS in patients who underwent LT for nonresectable CLM. MTV and TLG, which reflect the tumor burden and aggressiveness, were superior to conventional semiquantitative metrics (SUV_{max}, SUV_{mean}, SUV_{peak} and T/B-ratio) to predict OS and DFS in these patients. Even though not statistically significant, we observed a trend towards worsened OS and DFS in patients with SUVs and T/B-ratio over the cut-off value. To our knowledge, this is the first study to evaluate ^{18}F–FDG PET/CT as a prognostic tool in patients undergoing LT for CLM.

Several studies have shown that ^{18}F–FDG PET/CT can be utilized as a predictor of recurrence and overall prognosis after LT for HCC [29, 32–35]. Most of these studies have used only SUV_{max}, SUV_{mean} and T/B-ratio, and we have only identified one study which used MTV and TLG as prognostic indicators [29]. In this study Kim et al. showed that both T/B-ratio and TLG under cut-off value were significantly correlated to improved recurrence free survival after LT for HCC [29].

Previous studies on CRC have evaluated the prognostic value of ^{18}F–FDG PET/CT in non-transplanted patients, both in patient with and without liver metastases. In patients undergoing selective internal radiation therapy (SIRT) for CLM with yttrium-90, volumetric and metabolic information from ^{18}F–FDG PET/CT prior to the therapy is correlated to progression free survival and prognosis [27, 36–38]. ^{18}F–FDG PET/CT as post therapy evaluation was also a significant predictor of overall survival [37, 39]. Most of these studies have used MTV and TLG as indicators in addition to SUV_{max} and SUV_{peak}. Both Shady et al. (2016), Fedler et al. (2013) *and* Soydal *el al.* (2013) reported that MTV and TLG measured from ^{18}F–FDG PET/CT as response evaluation after SIRT for CLM predicted increased survival [27, 36, 37].

Metastatic CRC is considered a systemic disease. Total MTV and TLG reflect the tumor burden and metabolic activity, and it is likely to assume that high tumor burden and high metabolic activity increase the probability of extrahepatic metastatic disease not detected by ^{18}F–FDG PET/CT prior to the LT and leads to worsened prognosis. This is in agreement with our previous observations where other surrogate markers of advanced stage and aggressive tumor biology like high CEA levels and large tumor diameter prior to transplantation, were associated with decreased overall survival [8]. In the SECA patients, the site of recurrent disease seems to be more important than DFS, since patients with pulmonary relapse have better survival compared to patients developing lymph node or liver metastases [8, 40]. Thus, the ability of ^{18}F–FDG PET/CT to predict OS is clinically more important than DFS.

Our study has limitations. The small number of patients ($n = 23$) is a statistical weakness of this study. However, the SECA study is the only study of its kind worldwide, and despite that the number of patients was 23, the results showed significant differences for MTV and TLG under the cut-off value. It was performed retrospectively, and the protocol was not strictly controlled. There was varying time between imaging with ^{18}F–FDG PET/CT scan and LT that could have led to a progression of the disease in patients with a long interval. There was no difference in three and five-year OS in the patients with observation time from ^{18}F–FDG PET/CT to LT over the median compared to the patients with observation time under the median (data not shown). Furthermore, there was no difference in MTV and TLG between these groups (data not shown). Due to large tumor burden in some patients, it was difficult to place the ROI in the right liver lobe to measure background liver uptake. In these four cases, the ROI was placed in the left liver lobe. All patients received

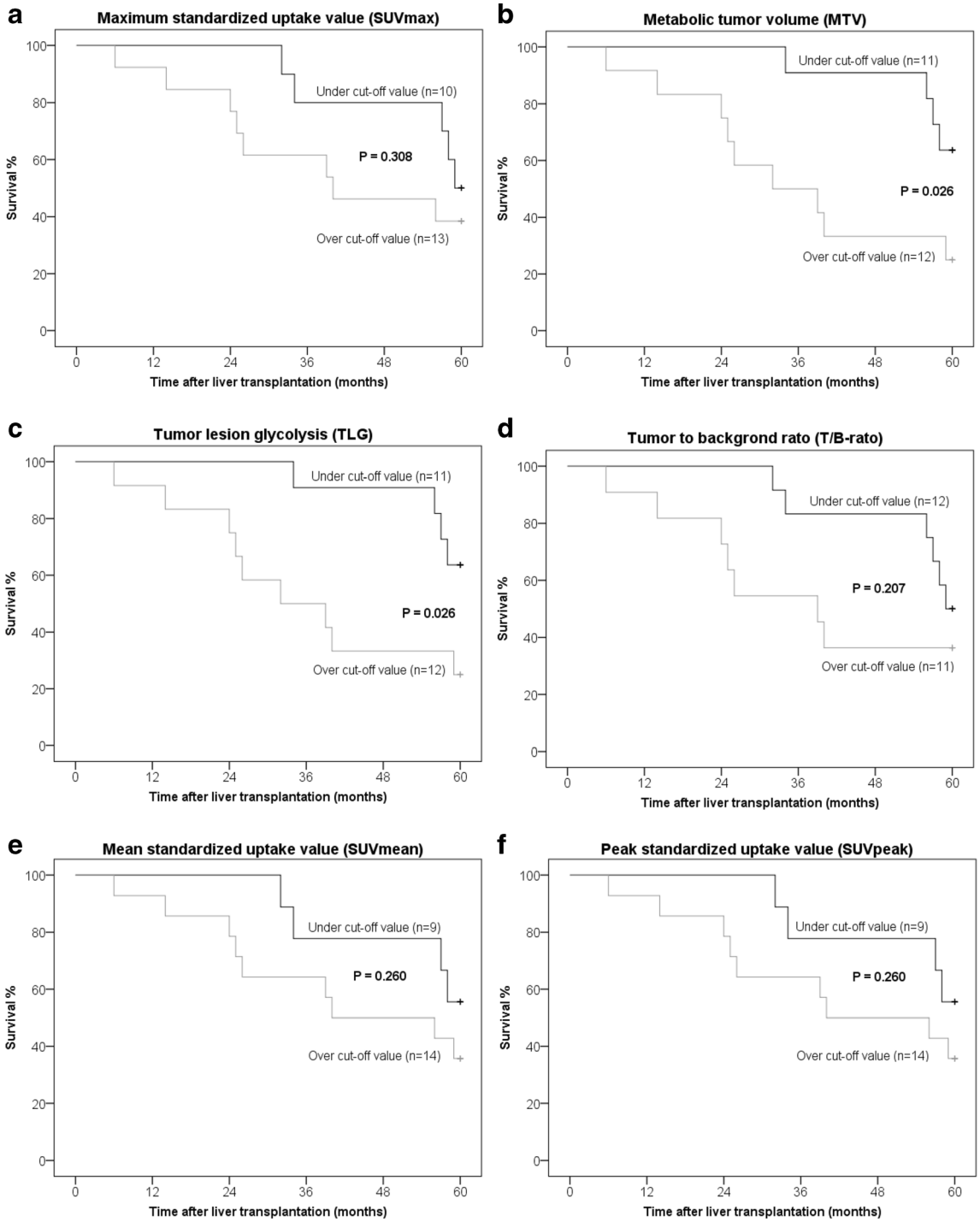

Fig. 1 Kaplan–Meier five-year overall survival (OS) plot. Patients with total metabolic tumor volume (**b**) and total lesion glycolysis (**c**) under cut-off value had significantly longer five-year OS than patients over cut-off value ($P = 0.027$ and 0.026, log rank test). Maximum standardized uptake value (**a**), tumor to background ratio (**d**), mean standardized uptake value (**e**) and peak standardized uptake value (**f**) were not significantly correlated to OS

chemotherapy prior to the preoperative ^{18}F–FDG PET/CT which could have affected the FDG uptake in the liver metastases. However, none of the patients received chemotherapy the last 4–6 weeks prior to the ^{18}F–FDG PET/CT. The cut-off values for the PET metrics determined by a ROC analysis will be highly dependent on the patient population, thus the specific cut-off values from this small study cannot be applied on other cohorts.

The ^{18}F–FDG PET performed in the SECA study followed a standard clinical protocol and was not optimized for the

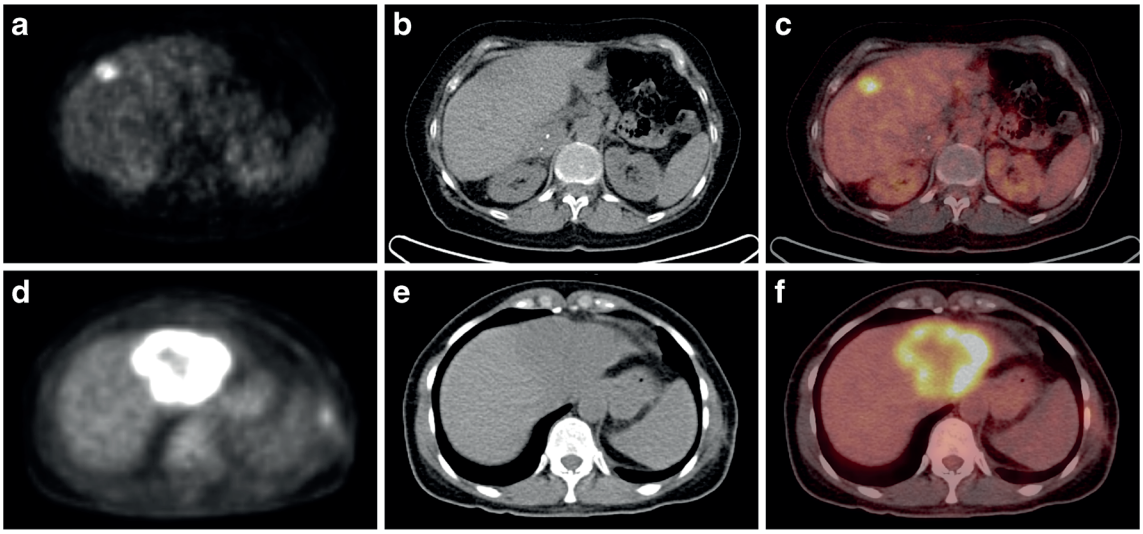

Fig. 2 **a-c** ^{18}F–FDG PET, CT and fused ^{18}F–FDG PET /CT images of a patient with total metabolic tumor volume (MTV) and total lesion glycolysis (TLG) under the cut-off value. SUV_{max}, SUV_{mean}, SUV_{peak} and T/B-ratio were over the cut-off (SUV_{max} 12.5 g/cm^3, SUV_{mean} 9.6 g/cm^3, SUV_{peak} 7.3 g/cm^3, T/B-ratio 5.3, MTV 14.4 cm^3, TLG 36.3 g). The patient is still alive ten years after liver transplantation (LT). **d-e** ^{18}F–FDG PET, CT and fused ^{18}F–FDG PET /CT images of a patient with total MTV and TLG over the cut-off value (SUV_{max} 15.8 g/cm^3, SUV_{mean} 9.3 g/cm^3, SUV_{peak} 12.9 g/cm^3, T/B-ratio 6.7, MTV 146.5 cm^3, TLG 1355.1 g). The patient died from recurrent disease two years after LT

imaging of liver metastases or for the detection of extra hepatic lesions in the liver hilum. Limited spatial resolution causing intensity diffusion [41] hampers the correct rendering of small lesions. Physiologic ^{18}F–FDG-uptake in the liver parenchyma, respiratory movements during acquisition causing smearing of focal ^{18}F–FDG uptakes and possible erroneous attenuation correction due to respiratory phase mismatch between the PET and CT data could have influenced the performance [42]. Since the SECA study, new PET/CT techniques have been introduced to cope with respiratory movements is increasingly used in clinical work, especially in radiation planning, but also to increase sensitivity of PET/CT in general [43]. Despite the fact that no optimized PET protocols were used for the imaging of liver metastases or for the detection of extra hepatic metastases in the liver hilum, the MTV and TLG measured from a standard ^{18}F–FDG PET protocol showed prognostic value in this patient population, underlining the relevance of this examination as a possible clinical selection tool.

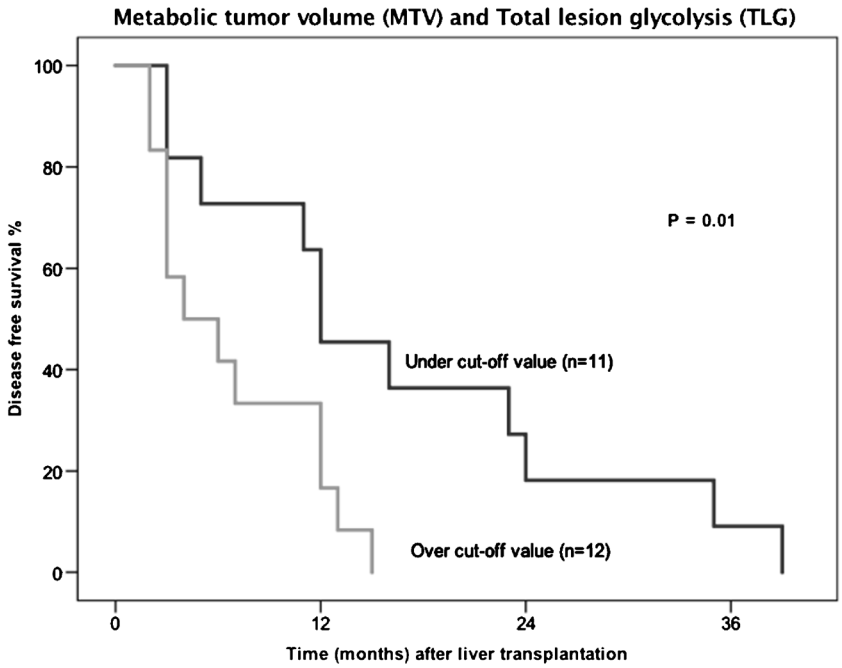

Fig. 3 Kaplan–Meier disease free survival (DFS) plot. Patients with total metabolic tumor volume (MTV) and total lesion glycolysis (TLG) under the cut-off value had significantly longer DFS compared to the patients over the cut-off value ($P = 0.01$, log rank test)

Conclusion

Total MTV and TLG from ^{18}F FDG PET/CT prior to LT for nonresectable CLM were significantly correlated to improved three and five-year OS and DFS and can potentially improve the patient selection for LT.

Compliance with ethical standards The authors declare no conflict of interest.

Informed consent was obtained from all individual participants included in the study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The SECA study was an open prospective study with institutional and regional ethical board approval (S-05409 Regional Ethics Committee. SECA study, ClinicalTrials.gov: NCT01311453).

References

1. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol. 2012;4:283–301. https://doi.org/10.2147/CLEP.S34285.
2. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334:693–9. https://doi.org/10.1056/NEJM199603143341104.
3. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10:35–43. https://doi.org/10.1016/S1470-2045(08)70284-5.
4. Masuoka HC, Rosen CB. Transplantation for cholangiocarcinoma. Clin Liver Dis. 2011;15:699–715. https://doi.org/10.1016/j.cld.2011.08.004.
5. Lee KK, Kim DG, Moon IS, Lee MD, Park JH. Liver transplantation versus liver resection for the treatment of hepatocellular carcinoma. J Surg Oncol. 2010;101:47–53. https://doi.org/10.1002/jso.21415.
6. Le Treut YP, Gregoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J, et al. Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. Ann Surg. 2013;257:807–15. https://doi.org/10.1097/SLA.0b013e31828ee17c.
7. Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. Transpl Int. 2008;21:1107–17. https://doi.org/10.1111/j.1432-2277.2008.00735.x.
8. Hagness M, Foss A, Line PD, Scholz T, Jorgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257:800–6. https://doi.org/10.1097/SLA.0b013e3182823957.
9. Briggs RH, Chowdhury FU, Lodge JP, Scarsbrook AF. Clinical impact of FDG PET-CT in patients with potentially operable metastatic colorectal cancer. Clin Radiol. 2011;66:1167–74. https://doi.org/10.1016/j.crad.2011.07.046.
10. Lin M, Wong K, Ng WL, Shon IH, Morgan M. Positron emission tomography and colorectal cancer. Crit Rev Oncol Hematol. 2011;77:30–47. https://doi.org/10.1016/j.critrevonc.2010.04.011.
11. Network NCC. National Comprehensive Cancer Network (NCCN) Guidelines Version 32017 Colon and Rectal Cancer 2017.
12. Bipat S, van Leeuwen MS, Comans EF, Pijl ME, Bossuyt PM, Zwinderman AH, et al. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis–meta-analysis. Radiology. 2005;237:123–31. https://doi.org/10.1148/radiol.2371042060.
13. Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. Eur J Nucl Med Mol Imaging. 2015;42:152–63. https://doi.org/10.1007/s00259-014-2930-4.
14. Patel S, McCall M, Ohinmaa A, Bigam D, Dryden DM. Positron emission tomography/computed tomographic scans compared to computed tomographic scans for detecting colorectal liver metastases: a systematic review. Ann Surg. 2011;253:666–71. https://doi.org/10.1097/SLA.0b013e31821110c9.
15. Ozis SE, Soydal C, Akyol C, Can N, Kucuk ON, Yagci C, et al. The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the primary staging of rectal cancer. World J Surg Oncol. 2014;12:26. https://doi.org/10.1186/1477-7819-12-26.
16. Thie JA. Understanding the standardized uptake value, its methods, and implications for usage. J Nucl Med. 2004;45:1431–4.
17. Tam HH, Cook GJ, Chau I, Drake B, Zerizer I, Du Y, et al. The role of routine clinical pretreatment 18F-FDG PET/CT in predicting outcome of colorectal liver metastasis. Clin Nucl Med. 2015;40:e259–64. https://doi.org/10.1097/rlu.0000000000000744.
18. Xia Q, Liu J, Wu C, Song S, Tong L, Huang G, et al. Prognostic significance of (18)FDG PET/CT in colorectal cancer patients with liver metastases: a meta-analysis. Cancer Imaging. 2015;15:19. https://doi.org/10.1186/s40644-015-0055-z.
19. Bai B, Bading J, Conti PS. Tumor quantification in clinical positron emission tomography. Theranostics. 2013;3:787–801. https://doi.org/10.7150/thno.5629.
20. Hyun SH, Choi JY, Shim YM, Kim K, Lee SJ, Cho YS, et al. Prognostic value of metabolic tumor volume measured by 18F-fluorodeoxyglucose positron emission tomography in patients with esophageal carcinoma. Ann Surg Oncol. 2010;17:115–22. https://doi.org/10.1245/s10434-009-0719-7.
21. Pan L, Gu P, Huang G, Xue H, Wu S. Prognostic significance of SUV on PET/CT in patients with esophageal cancer: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2009;21:1008–15. https://doi.org/10.1097/MEG.0b013e328323d6fa.
22. Al-Sarraf N, Gately K, Lucey J, Aziz R, Doddakula K, Wilson L, et al. Clinical implication and prognostic significance of standardised uptake value of primary non-small cell lung cancer on positron emission tomography: analysis of 176 cases. Eur J Cardiothorac Surg. 2008;34:892–7. https://doi.org/10.1016/j.ejcts.2008.07.023.
23. Downey RJ, Akhurst T, Gonen M, Vincent A, Bains MS, Larson S, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. J Clin Oncol. 2004;22:3255–60. https://doi.org/10.1200/JCO.2004.11.109.
24. Zhang H, Wroblewski K, Appelbaum D, Pu Y. Independent prognostic value of whole-body metabolic tumor burden from FDG-PET in non-small cell lung cancer. Int J Comput Assist Radiol Surg. 2013;8:181–91. https://doi.org/10.1007/s11548-012-0749-7.
25. Dibble EH, Alvarez AC, Truong MT, Mercier G, Cook EF, Subramaniam RM. 18F-FDG metabolic tumor volume and total glycolytic activity of oral cavity and oropharyngeal squamous cell cancer: adding value to clinical staging. J Nucl Med. 2012;53:709–15. https://doi.org/10.2967/jnumed.111.099531.
26. Higgins KA, Hoang JK, Roach MC, Chino J, Yoo DS, Turkington TG, et al. Analysis of pretreatment FDG-PET SUV parameters in

head-and-neck cancer: tumor SUVmean has superior prognostic value. Int J Radiat Oncol Biol Phys. 2012;82:548–53. https://doi.org/10.1016/j.ijrobp.2010.11.050.

27. Shady W, Kishore S, Gavane S, Do RK, Osborne JR, Ulaner GA, et al. Metabolic tumor volume and total lesion glycolysis on FDG-PET/CT can predict overall survival after (90)Y radioembolization of colorectal liver metastases: A comparison with SUVmax, SUVpeak, and RECIST 1.0. Eur J Radiol. 2016;85:1224–31. https://doi.org/10.1016/j.ejrad.2016.03.029.
28. Ogawa S, Itabashi M, Kondo C, Momose M, Sakai S, Kameoka S. Prognostic Value of Total Lesion Glycolysis Measured by 18F-FDG-PET/CT in Patients with Colorectal Cancer. Anticancer Res. 2015;35:3495–500.
29. Kim YI, Paeng JC, Cheon GJ, Suh KS, Lee DS, Chung JK, et al. Prediction of Posttransplantation Recurrence of Hepatocellular Carcinoma Using Metabolic and Volumetric Indices of 18F-FDG PET/CT. J Nucl Med. 2016;57:1045–51. https://doi.org/10.2967/jnumed.115.170076.
30. Gulec SA, Suthar RR, Barot TC, Pennington K. The prognostic value of functional tumor volume and total lesion glycolysis in patients with colorectal cancer liver metastases undergoing 90Y selective internal radiation therapy plus chemotherapy. Eur J Nucl Med Mol Imaging. 2011;38:1289–95. https://doi.org/10.1007/s00259-011-1758-4.
31. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50(Suppl 1):122S–50S. https://doi.org/10.2967/jnumed.108.057307.
32. Bailly M, Venel Y, Orain I, Salame E, Ribeiro MJ. 18F-FDG PET in Liver Transplantation Setting of Hepatocellular Carcinoma: Predicting Histology? Clin Nucl Med. 2016;41:e126–9. https://doi.org/10.1097/rlu.0000000000001040.
33. Detry O, Govaerts L, Deroover A, Vandermeulen M, Meurisse N, Malenga S, et al. Prognostic value of (18)F-FDG PET/CT in liver transplantation for hepatocarcinoma. World J Gastroenterol. 2015;21:3049–54. https://doi.org/10.3748/wjg.v21.i10.3049.
34. Lee SD, Kim SH, Kim YK, Kim C, Kim SK, Han SS, et al. (18)F-FDG-PET/CT predicts early tumor recurrence in living donor liver transplantation for hepatocellular carcinoma. Transpl Int. 2013;26:50–60. https://doi.org/10.1111/j.1432-2277.2012.01572.x.
35. Lin CY, Liao CW, Chu LY, Yen KY, Jeng LB, Hsu CN, et al. Predictive Value of 18F-FDG PET/CT for Vascular Invasion in Patients With Hepatocellular Carcinoma Before Liver Transplantation. Clin Nucl Med. 2017;42:e183–e7. https://doi.org/10.1097/RLU.0000000000001545.
36. Fendler WP, Philippe Tiega DB, Ilhan H, Paprottka PM, Heinemann V, Jakobs TF, et al. Validation of several SUV-based parameters derived from 18F-FDG PET for prediction of survival after SIRT of hepatic metastases from colorectal cancer. J Nucl Med. 2013;54:1202–8. https://doi.org/10.2967/jnumed.112.116426.
37. Soydal C, Kucuk ON, Gecim EI, Bilgic S, Elhan AH. The prognostic value of quantitative parameters of 18F-FDG PET/CT in the evaluation of response to internal radiation therapy with yttrium-90 in patients with liver metastases of colorectal cancer. Nucl Med Commun 2013;34:501-506. doi:https://doi.org/10.1097/MNM.0b013e32835f9427.
38. Zerizer I, Al-Nahhas A, Towey D, Tait P, Ariff B, Wasan H, et al. The role of early (1)(8)F-FDG PET/CT in prediction of progression-free survival after (9)(0)Y radioembolization: comparison with RECIST and tumour density criteria. Eur J Nucl Med Mol Imaging. 2012;39:1391–9. https://doi.org/10.1007/s00259-012-2149-1.
39. Sabet A, Meyer C, Aouf A, Sabet A, Ghamari S, Pieper CC, et al. Early post-treatment FDG PET predicts survival after 90Y microsphere radioembolization in liver-dominant metastatic colorectal cancer. Eur J Nucl Med Mol Imaging. 2015;42:370–6. https://doi.org/10.1007/s00259-014-2935-z.
40. Hagness M, Foss A, Egge TS, Dueland S. Patterns of recurrence after liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg Oncol. 2014;21:1323–9. https://doi.org/10.1245/s10434-013-3449-9.
41. Kapoor V, McCook BM, Torok FS. An introduction to PET-CT imaging. Radiographics. 2004;24:523–43. https://doi.org/10.1148/rg.242025724.
42. Pettinato C, Nanni C, Farsad M, Castellucci P, Sarnelli A, Civollani S, et al. Artefacts of PET/CT images. Biomedical Imaging and Intervention Journal. 2006;2:e60. https://doi.org/10.2349/biij.2.4.e60.
43. Chi A, Nguyen NP. 4D PET/CT as a Strategy to Reduce Respiratory Motion Artifacts in FDG-PET/CT. Front Oncol. 2014;4:205. https://doi.org/10.3389/fonc.2014.00205.