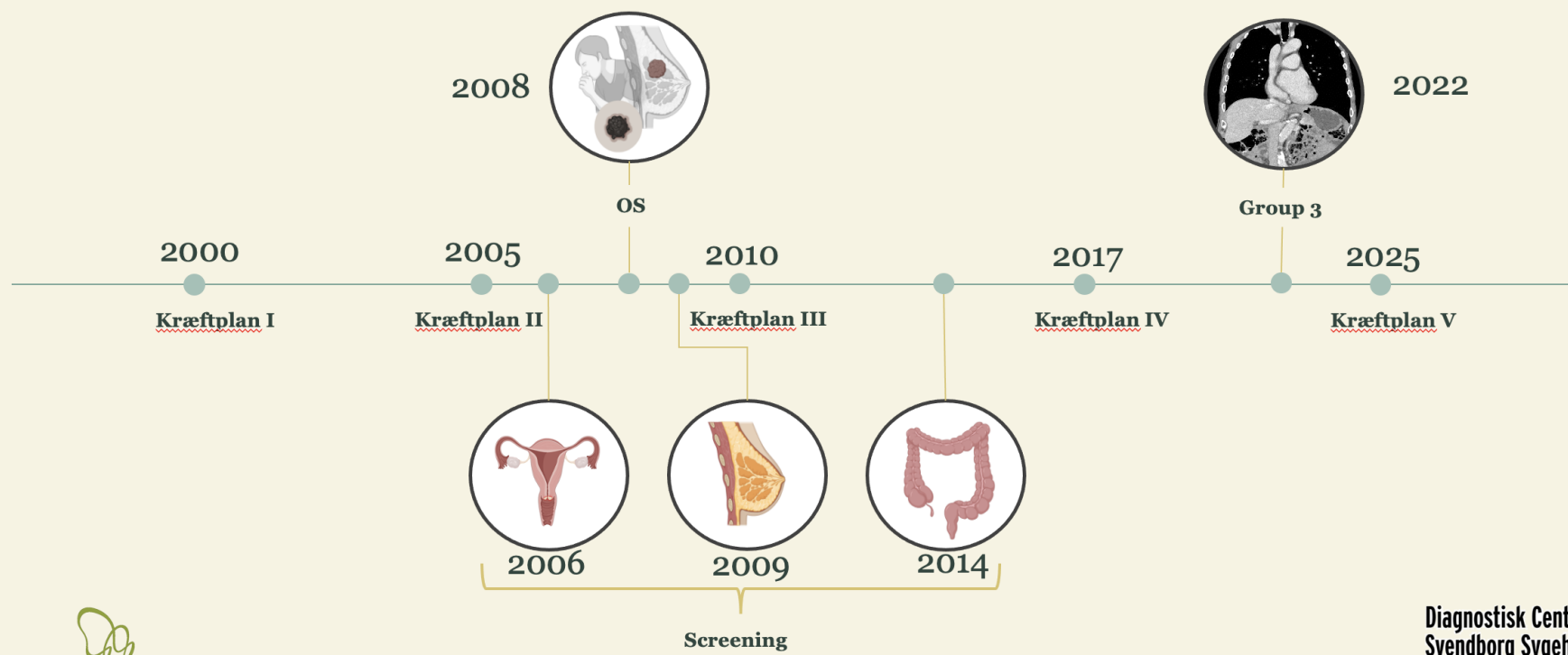


Diagnostic Centre, Svendborg Hospital, Odense University Hospital
Perspectives & Cases

Peter Thye-Rønn
leading physician, PhD

Cancer investigation in Denmark



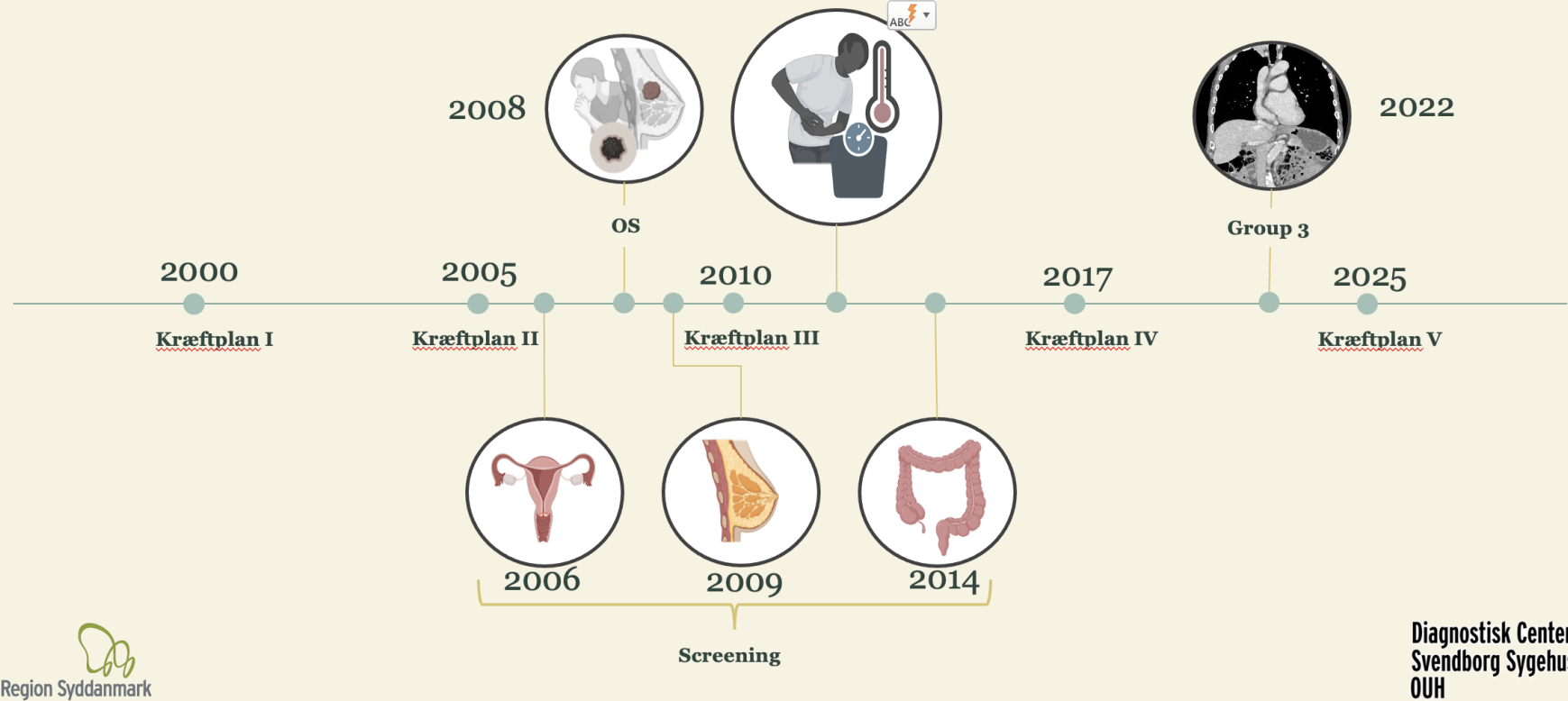
Diagnostisk Center
Svendborg Sygehus
OUH

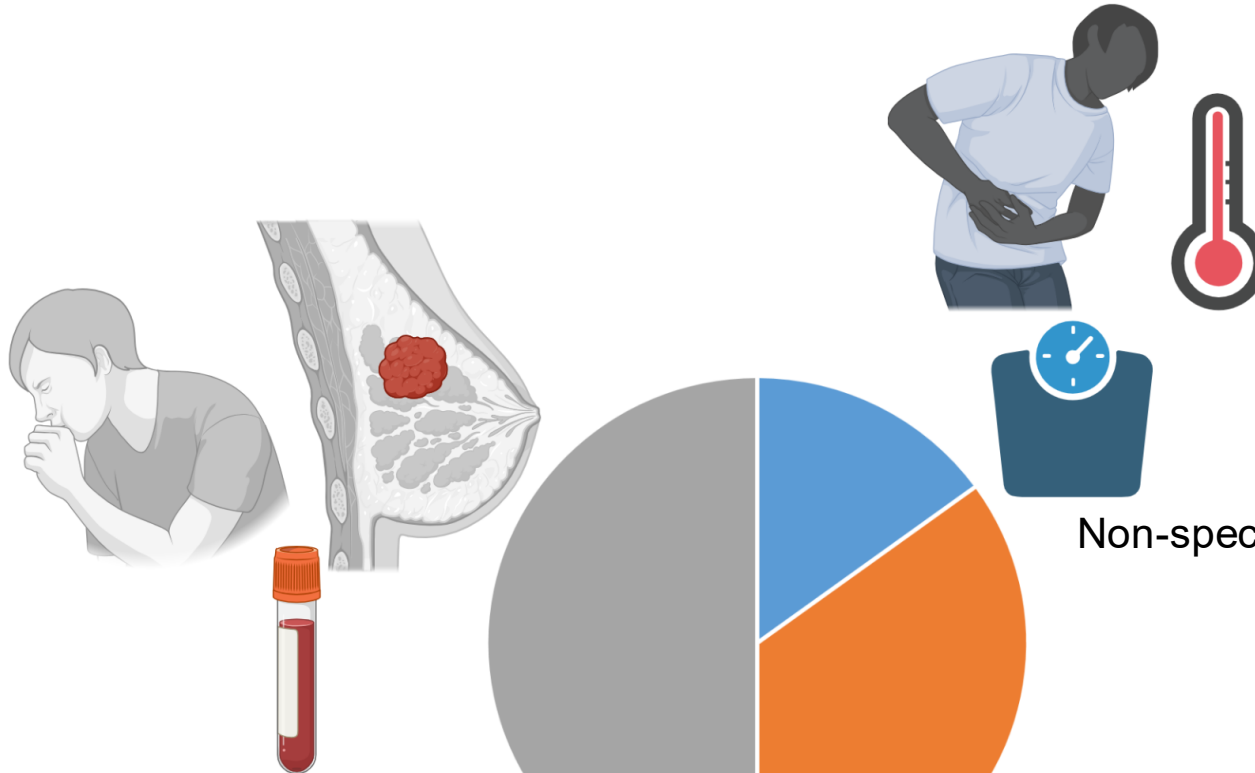


OUH
Odense Universitetshospital
Svendborg Sygehus

Cancer investigation in Denmark

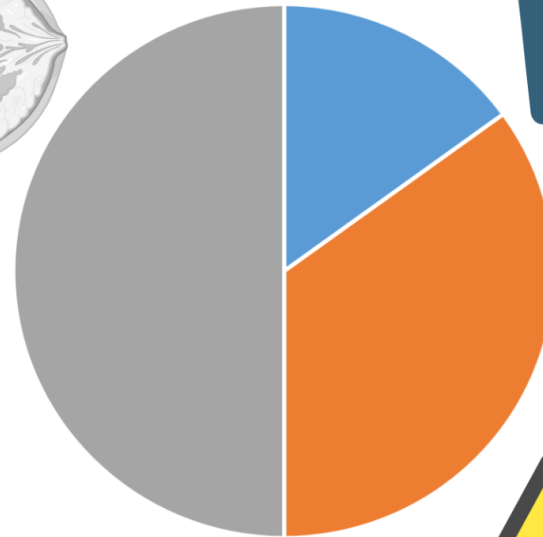
Diagnostic Package – 2012 + rev. 2022





Group 1

Organspecific symptoms
≈50%



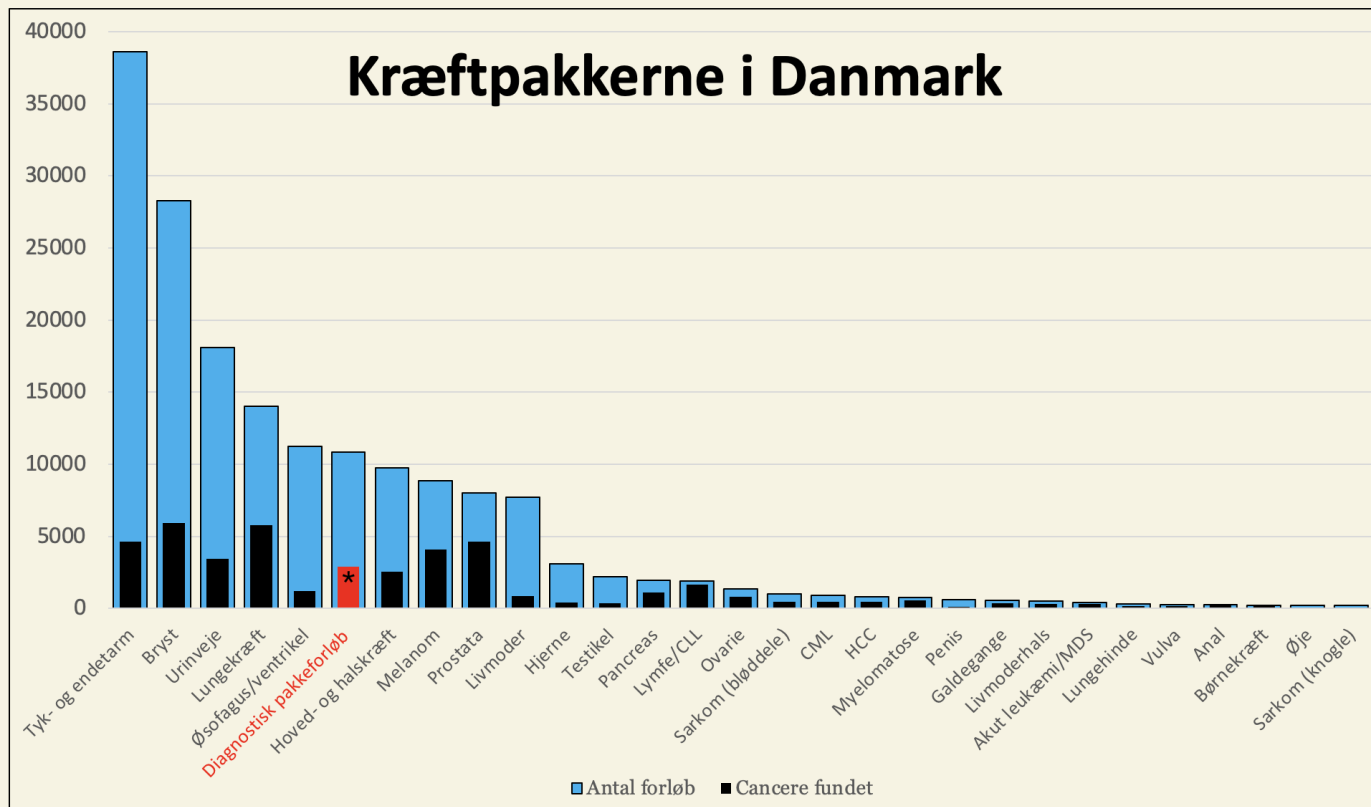
Group 2

Non-specific Signs and Symptoms
NSSC
≈10-20%



Group 3
Vague symptoms
≈30-40%

Kræftpakkerne i Danmark



*Andel fundne cancers er estimeret ud fra BJC, 2024. doi:10.1038/s41416-024-02620-y samt ikke publicerede MUP data

Årsopgørelse 2024, Sundhedsdatastyrelsen
13. juni 2025

MUP history(DK)

2014 + 2022 – SST.DK



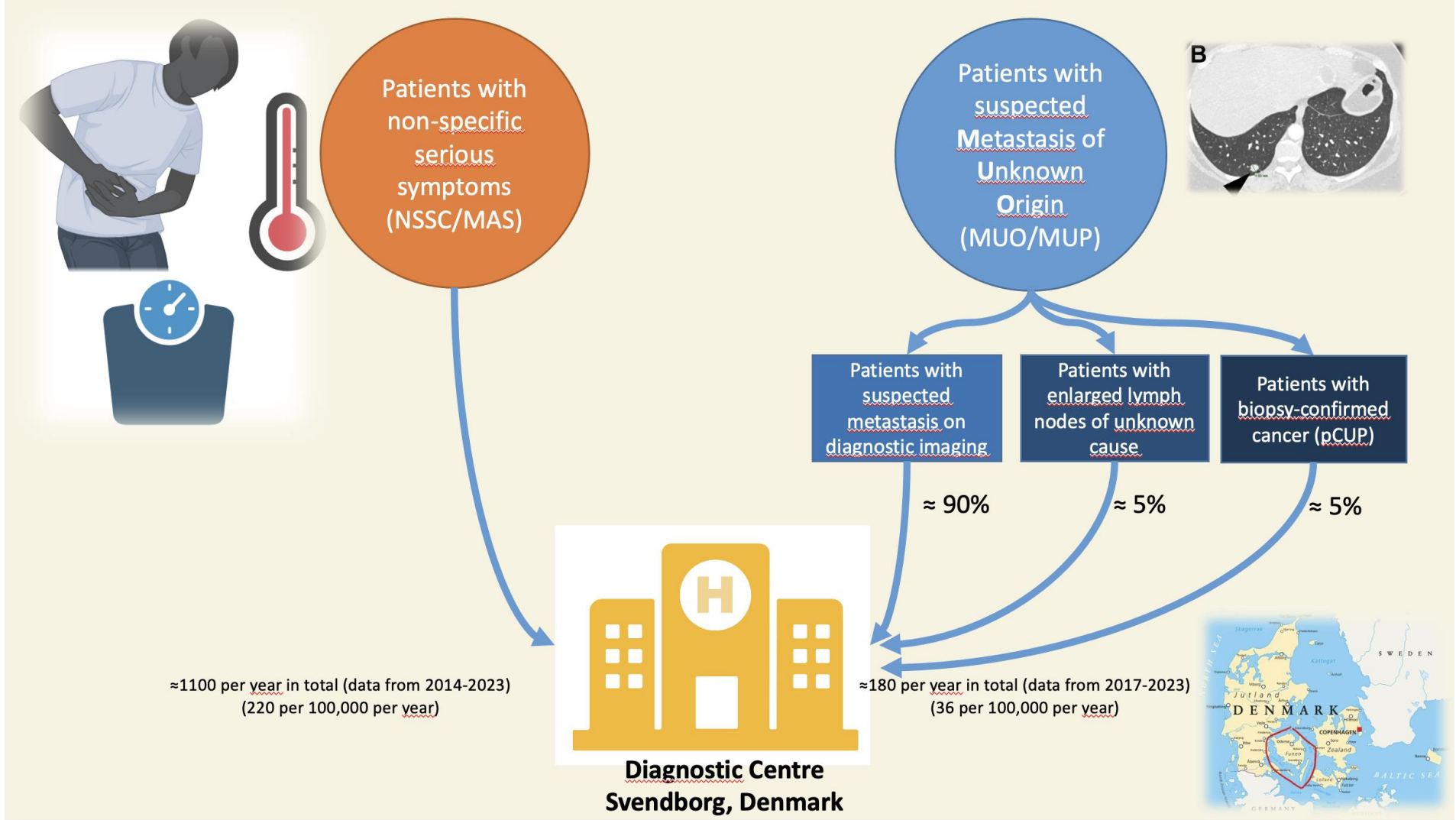
”Forud for henvisning til Diagnostisk pakkeforløb vil der typisk være rejst mistanke om metastasesuspekter forandringer eller metastaser uden kendt primær tumor ved billeddiagnostiske fund af en suspekt forandring eller ved palpation af patologisk forstørrede lymfeknuder uden anden forklaring. I nogle tilfælde vil fund af maligne celler/væv i biopsi være første tegn på kræft (metastase).”

Fund der kan føre til henvisning til DC, hvor der ellers ikke er tegn på primærtumor:

- Levermetastaser uden samtidig mistanke om HCC eller CRC.
- Knoglemetastaser
- Lymfadenopati (dog fraset på hals og hos kvinder i armhulen, samt af oplagt infektiøs ætiologi)
- Hjernemetastaser (fraset hvis de allerede er i forløb hos neurologerne)
- Karcinomatose
- Retroperitoneal forandringer
- Andre forandringer ikke angivet ovenfor

DC Unit – “tools” available locally?

- DC unit (500.000 inhabitants, OUH)
- Radiology (Svendborg)
- Nuclear Medicine (Odense)
- Broad internal medical unit (M/FAM)
 - Rheumatology (eg. vascular ultrasound)
 - Gastroenterology incl. Surgeons
 - Etc.
- MDT conferences (all specialties incl. **MUP-MDT**)
- DP - package meetings at OUH (all relevant departments)
- ChatGPT, “text mining”?



Case 1 – MUP

- 60-year-old woman, previously healthy, being investigated due to bloating and abdominal distention. PET/CT on 4/9/25 showing wall thickening in the transverse colon, as well as inhomogeneous pathological increased FDG uptake in the carcinomatous suspect paracolic area extending from the left colon flexure towards the right to the cecum. Colonoscopy i.a.
- Onkogyn. deny gynecological cancer (CA125 110).
- **Plan?**

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- Rp. UL biopsi (dept. of radiology) – failed!
- Rp. CT assisted biopsi (OUH) + Surgeons laparoscopic biopsi
- **ChatGPT:** “The findings in the PET/CT scan, describing wall thickening in the transverse colon and inhomogeneous pathological FDG uptake in the paracolic region, are concerning for malignancy, specifically **colorectal cancer (CRC)**”

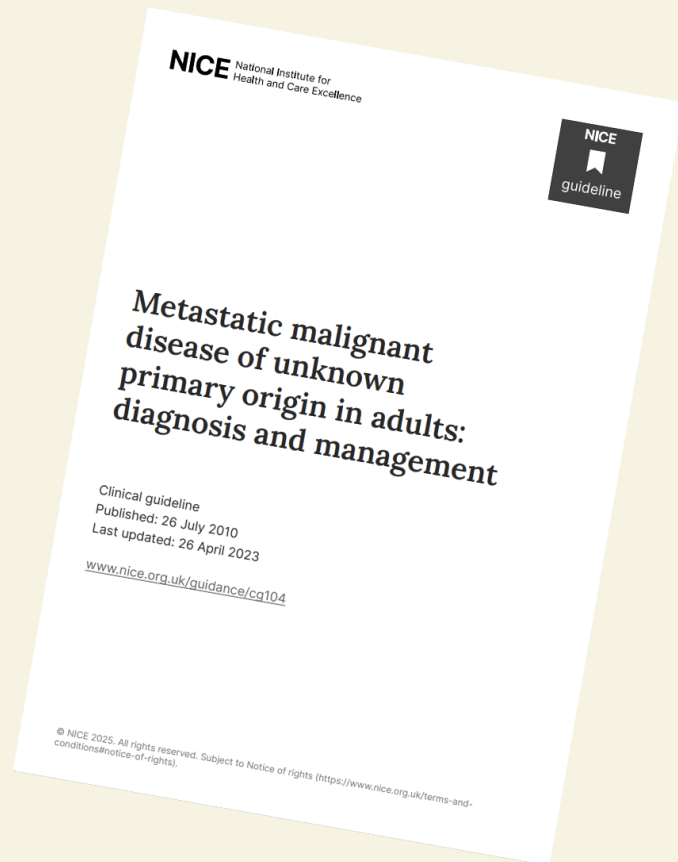
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- Rp. CT assisted biopsi (OUH) + Surgeons laparoscopic biopsi
- **/Adenocarcinoma high grade/**
 - rp. Gynecological department

MUP history

(Suspicion of Metastasis of Unknown Primary)

2010 – UK NICE



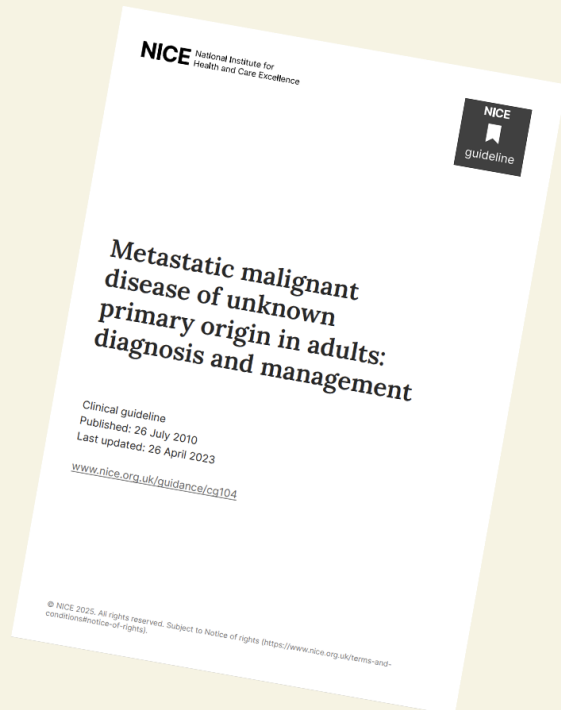
“Every hospital with a cancer centre or unit should establish a carcinoma of unknown primary (CUP) team. Ensure that patients have access to the team when a malignancy of undefined primary origin (MUO) is diagnosed.”

The team should as a minimum consist of:

- an oncologist,
- a palliative care physician
- A CUP specialist nurse or key worker

MUP history

2010 – UK NICE



Definition: NICE i 2010:

Malignancy of undefined primary origin (MUO):

Metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation.

Provisional carcinoma of unknown primary (provisional CUP):

Metastatic epithelial or neuroendocrine malignancy identified on the basis of histology/cytology, with no primary site detected despite a selected initial screen of investigations, before specialist review and possible further specialised investigations.

Confirmed carcinoma of unknown primary (confirmed CUP):

Metastatic epithelial or neuroendocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialised investigations as appropriate.

MUP history

2010 – UK NICE



Defineret af NICE i 2010:

Malignancy of undefined primary origin (MUO):

Metastatic epithelial or mesenchymal malignancy identified on the basis of a limited number of histological investigations, before specialist review and possible further specialised investigations. **Mistænkt cancer ud fra billeddiagnostik og/eller objektive kliniske fund**

Provisional carcinoma of unknown primary (provisional CUP):

Metastatic epithelial or mesenchymal malignancy identified on the basis of histological investigations, before specialist review and possible further specialised investigations. **Histologisk påvist cancer, men hvor udredningen ikke er færdiggjort**

Confirmed carcinoma of unknown primary (confirmed CUP):

Metastatic epithelial or mesenchymal malignancy identified on the basis of final histological investigations, despite a selected initial specialist review, and further specialised investigations as appropriate. **Histologisk påvist cancer, hvor udredningen er færdiggjort**

SPECIAL ARTICLE

Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up²³

A. Krämer^{1,2}, T. Bochtler^{1,2,3}, C. Paul^{4,5}, G. Baciarello⁶, S. Delorme⁷, K. Hemminki^{8,9}, L. Mileskin¹⁰, H. Moch^{5,6}, K. Oien¹¹, T. Olivier^{12,13}, A. Patrikidou¹⁴, H. Wasan¹⁵, G. Zarkavelis¹⁶, G. Pentheroudakis¹⁷ & K. Fizazi¹⁴ on behalf of the ESMO Guidelines Committee

¹Clinical Cooperation Unit Molecular Haematology/Oncology, German Cancer Research Center (DKFZ) Heidelberg; ²Department of Internal Medicine V, University of Heidelberg, Heidelberg; ³Department of Medical Oncology, National Center for Tumor Diseases (NCT), University of Heidelberg, Heidelberg, Germany; ⁴Department of Pathology and Molecular Pathology, University Hospital Zurich (USZ), Zurich; ⁵Medical Faculty, University of Zurich (UZH), Zurich, Switzerland; ⁶Department of Epidemiology, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy; ⁷Division of Radiology, German Cancer Research Center (DKFZ), Heidelberg; ⁸Medical Oncology Department, German Cancer Research Center (DKFZ), Heidelberg, Germany; ⁹Faculty of Medicine and Biomedical Center, Charles University, Pilsen, Czech Republic; ¹⁰Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; ¹¹Institute of Cancer Sciences, University of Glasgow, Glasgow, UK; ¹²Department of Oncology, Geneva University Hospital, Geneva, Switzerland; ¹³Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, USA; ¹⁴Department of Cancer Medicine, Institute Gustave Roussy, University of Paris Saclay, Villejuif, France; ¹⁵Department of Cancer Medicine, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; ¹⁶Department of Medical Oncology, University of Ioannina, Ioannina, Greece; ¹⁷European Society for Medical Oncology, Lugano, Switzerland

Available online 20 December 2022

Key words: Classification, ESMO Clinical Practice Guideline, diagnosis, risk assessment, treatment, unknown primary neoplasm

INCIDENCE AND EPIDEMIOLOGY

Definition

Cancer of unknown primary (CUP) is defined as a carcinoma or undifferentiated neoplasm for which a standardised diagnostic work-up fails to identify the primary tumour responsible for metastatic seeding.

Incidence

CUP accounts for <5% of cancers but, because of its high mortality rate, its relative contribution to cancer deaths is higher.¹ The incidence of CUP has been declining, probably due to improving success in localising primary tumours.² The incidence increases with age and is higher in men compared with women. Adenocarcinoma is the most common histology. Approximately 50% of CUP cases can be categorised as well-differentiated to moderately differentiated adenocarcinomas, ~30% as poorly differentiated adenocarcinomas or undifferentiated carcinomas, ~15% as squamous-cell carcinomas and ~5% as undifferentiated neoplasms.^{2,3} Sarcomas, melanomas,

germ cell tumours, neuroendocrine tumours and haematological malignancies whose exact site of origin is not established are not included in the CUP definition. Many patients present with metastases in multiple organs, such as the liver (most common), respiratory system, lymph nodes, abdominal cavity, bone and brain.² The decrease in CUP incidence has been noted for most metastatic locations and histologies.¹

Subsequent primary cancers after CUP

CUP diagnostics include a meticulous search for the hidden primary cancer, which explains why no new primaries are diagnosed soon after a CUP diagnosis.⁴ The majority of patients with CUP will not have a primary lesion identified during the course of the disease. However, some survivors of CUP may develop (i) initially hidden primary tumours responsible for their metastatic disease or (ii) second primary cancers. Elevated risks for the development of second primary risks observed for cancers of several types of organs and aerodigestive tract, with the highest being observed for the development of non-Hodgkin's lymphoma and squamous-cell skin cancer, which are known hallmarks of dysregulated immunity, suggesting a contribution of suppressed immune function as a feature of CUP.

Risk factors

Smokers are at risk of developing CUP and this risk correlates with the level of tobacco exposure: from 1.8-fold for smokers

^{*}Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Geneva 4, 6900 Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

[†]Note: Approved by the ESMO Guidelines Committee: April 2022, last update November 2022. This publication supersedes the previously published version—*Ann Oncol*. 2015;26(suppl 5):v133-v138.
0923-7528/© 2022 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.

ESMO guidelines, Krämer et al. 2023

Case 2

- 13/9: 67-year-old man with type 2 diabetes. Admitted with severely elevated CRP. Suspected primary infection, but all cultures have been negative. PET CT inconclusive, and therefore large vessel vasculitis and/or GCA have been ruled out. Normal UL. Lumbar puncture also without signs of infection, and thus the most likely tentative diagnosis is medication side effects. This can be seen with atorvastatin and is considered the most likely. Discharge planned for 14/9 after blood tests and rounds.
- Follow-up at the Diagnostic Center.
- **ChatGPT:** “Based on the information provided, the most likely diagnosis seems to be **medication side effects**, particularly from **atorvastatin**, which is mentioned as the most likely cause.”

Case 2

25/9: He is still feeling unwell and is very tired. We are discussing the results of the remaining blood tests from the recent hospitalization, including neurofilament light polypeptide, which is slightly elevated.

In light of the medical note from 12/9-25, where there was a consultation with the neurologist on the blood test, including neurofilament, it is noted that if symptoms persist, a follow-up with neurology is desired for EMG/ENG. I have therefore decided to refer to the neurologists. Otherwise, I will continue the planned course of action with us.."

Case 2

1/10: DC.

Normal PET/CT scan. All microbiological tests negative, and primary suspicion is medication side effects. Initially, there was no clear indication of GCA (Giant Cell Arteritis) at the time of admission. He is now here for follow-up on blood tests and further clinical evaluation.

I have received expert help from rheumatologists, who performed vascular ultrasound (second time) and found signs in the distal temporal arteries that are fully consistent with GCA.

The clinical picture remains unchanged with elevated CRP around 100 and significant inflammatory condition.

Prescription: Prednisolone 60 mg and DXA scan recommended.

Case 3

- **7/10:** 70-year-old male referred to the Diagnostic Center as an MUP patient from the Spine Center due to multiple bone metastases in the spine, including a near-transverse fracture at L3. He has severe COPD stage 4. Spine surgeons are unable to offer stabilizing surgery due to the severe COPD condition. A CT-TAB was performed on 07.10 and a supplementary FDG-PET on 15.10, showing possible signs of a primary tumor. Please evaluate at the MUP-MDT on 16.10 for further investigation – either through a CFL-registry examination or CT-guided biopsy.
- The oncologists will not offer treatment before the histological diagnosis is confirmed, including not providing palliative radiotherapy.

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Case 3

- A low-dose FDG PET scan showing the same changes as the CT scan from 07/10, but with an additional suspicious FDG uptake several bone foci including columna, adrenal glands and the right lung hilus, possibly indicating a primary tumor.
- The patient will be referred to the MUP-MDT on 16/10 for further planning, including possible biopsy from the CFL clinic.

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Case 3 – MUP MDT

- **16/10:** There is a threatening transverse fracture at L3 and no obvious primary tumor seen on the CT-TAB performed on 07.10 or the PET/CT on 15.10. These are interpreted as nonspecific changes consistent with chronic severe COPD, with weak FDG activity in the right lung hilus. There is bilateral adrenal enlargement, most pronounced on the right side with intense FDG uptake.
- Paraclinically, PSA is 6.0. No suspicion of primary lung cancer or prostate cancer is found, but there is a general indication for a prompt CT-guided biopsy from one of the several bone foci with the aim of offering palliative radiotherapy.
- Department R can already offer radiotherapy, but this requires a prior urgent biopsy result.

Case 3 - ChatGPT

- **1. Metastatic Bone Disease (likely from a primary cancer)**
- **Primary tumor:** The patient has multiple bone metastases, including a threatening transverse fracture at L3. This suggests that there may be a primary cancer elsewhere in the body. However, the CT and PET/CT scans did not identify an obvious primary tumor, which makes the source of metastasis difficult to pinpoint at this stage.
- **Possible primary sources:** Common cancers that metastasize to bone include prostate cancer, lung cancer, breast cancer, and kidney cancer. However, a primary lung tumor or prostate cancer is not strongly suspected based on current findings.
- **2. Adrenal Metastasis or Primary Adrenal Disease**
- The presence of bilateral adrenal enlargement, with significant FDG uptake in the right adrenal gland, raises concern for **adrenal metastasis** from a primary cancer. The bilateral enlargement and FDG activity suggest that the adrenals may be involved in the metastatic spread, *although primary adrenal tumors (such as adrenal cortical carcinoma) are less common.*
- ETC....

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Case 3

- **21/10:** Contact with pathologist – questionable material in terms of flow cytometry. Abnormal cells are observed, consistent with malignancy. Suspected hematologic neoplasm, no suspicion of small cell carcinoma. The patient's performance status is 3-4. Even if lymphoma is confirmed, it is considered that the patient would benefit from palliative radiotherapy for the threatening transverse fracture.
- **27/10:** Pathology result from L2 – the diagnosis is metastasis from adrenocortical carcinoma with a Ki-67 index of 90%. On the PET/CT from 15/10, there was also FDG uptake in the right adrenal gland, so both imaging and histopathology now confirm the diagnosis. This is an extraordinarily rare disease with a poor prognosis.
- Potential palliative measures, as the patient is not a candidate for systemic oncological treatment.
- **30/10:** The patient has been declared terminal, and an application for terminal drug allowance has been submitted. Currently, there are no complex issues, but the family is advised to contact their general practitioner if needed.

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UK

≈62 enheder investigates MUP+CUP

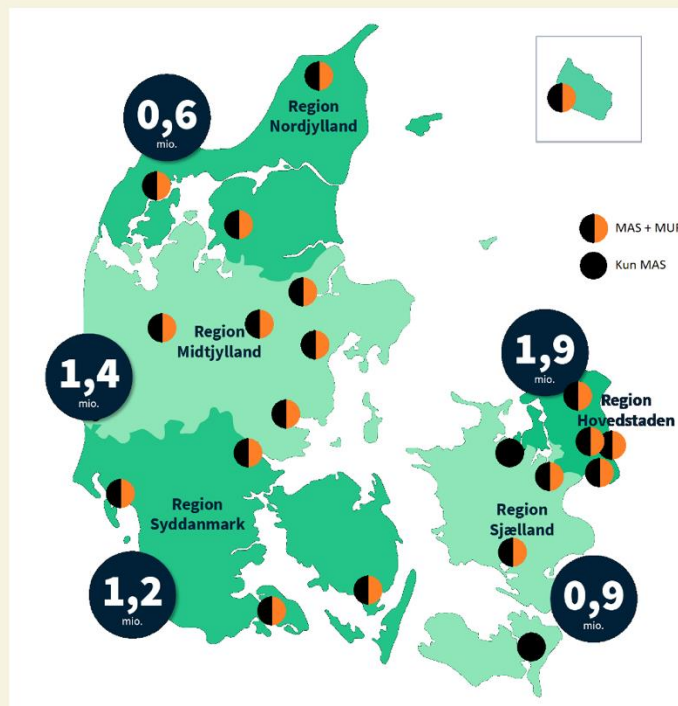
Since 2010



Danmark

21 DC most investigate MUP+pCUP-patients

Since 2014



Sverige+Norge

Unclear role for DC's in MUP+CUP

Since 2015



MUP publication DC Svendborg 2026

| | Stares et al. | van Mourik et al. | Ando et al. | Grønnemose et al. |
|---------------------|---------------------------|---------------------------|---------------------------|-------------------|
| Udgivet | 2021 | 2023 | 2023 | 2026* |
| Journal | British Journal of Cancer | British Journal of Cancer | Int. J. Clinical Oncology | EJC/BJC |
| Antal | n = 1225 | n = 361 | n = 407 | n= 1106 |
| Data period | 2010-2020 | 2014-2020 | 2012-2020 | 2017-2024 |
| Referred as MUO | 1225 | 239 | 57 | 1040 |
| Referred as pCUP | 0 | 122 | 350 | 64 |
| Referral population | 1.5M | 27.2M | 16M | 0.5M |
| Location | Scotland | Australia | Japan | Danmark |
| Per 100.000 per år | 8,2 | 0,2 | 0,3 | 31,5 |

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Perspectives:

- Multidisciplinary function
- Ultrasound vasculare on site
- MUP MDT (pCUP/cCUP)
- Coordination between primary and secondary sectors



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E-mail: Peter.Thye-Ronn@rsyd.dk